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(FILE 'HCAPLUS' ENTERED AT 10:17:02 ON 22 FEB 2001)
DEL HIS Y

FILE 'REGISTRY' ENTERED AT 10:19:52 ON 22 FEB 2001
E NITRIC OXIDE/CN

L1 1 S E3
E NITRIC OXIDE SYTHETASE/CN
E NITRIC OXIDE SYNTHASE
E NITRIC OXIDE SYNTHASE/CN
L2 1 S E3

FILE 'HCAPLUS' ENTERED AT 10:20:53 ON 22 FEB 2001

L3 4191 S IL 12 OR INTERLEUKIN 12
L4 11519 S ADJUVANT#
L5 125212 S L1 OR L2 OR (NO OR NITRIC OXIDE)
L6 142 S L3 (L) L4
L7 9442 S IMMUNOSTIM?
L8 84 S L6 AND L7
L9 2 S L8 AND L5
L10 4 S L6 AND L5
L11 7 S L3 AND L4 AND L5

FILE 'REGISTRY' ENTERED AT 10:22:54 ON 22 FEB 2001
L12 2 S 50903-99-6 OR 17035-90-4

FILE 'HCAPLUS' ENTERED AT 10:23:18 ON 22 FEB 2001

L13 1678 S L12
L14 875 S L NAME OR L NMMA
L15 1774 S L13 OR L14
L16 0 S L6 AND L15
L17 2 S L3 AND L14
L18 25593 S VACCINE#
L19 441 S L3 AND L18
L20 12 S L19 AND L5
L21 1 S L19 AND L14
L22 15 S L9 OR L10 OR L11 OR L17 OR L21 OR L20
L23 3172 S IMMUN? (3A) STIMUL?
L24 58 S L3 AND L23
L25 3 S L24 AND (L14 OR L5)
L26 16 S L25 OR L22

FILE 'USPATFULL' ENTERED AT 10:28:48 ON 22 FEB 2001

L27 1535 S L1 OR L2
L28 65 S L12
L29 1550 S L27 OR L28
L30 4119 S NITRIC OXIDE OR L NAME OR L NMMA
L31 705 S (INTERLEUKIN 12 OR IL12 OR IL 12)
L32 130 S (INTERLEUKIN 12 OR IL12 OR IL 12)/CLM
L33 9 S L32 AND L30
L34 136 S (INTERLEUKIN 12 OR IL12 OR IL 12)/CLM, TI, AB
L35 9 S L34 AND (L29 OR L30)
L36 9 S L33 OR L35

FILE 'USPATFULL, HCAPLUS' ENTERED AT 10:32:18 ON 22 FEB 2001

Prasad 09/395,038

L37

25 DUP REM L36 L26 (0 DUPLICATES REMOVED)

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FILE 'REGISTRY' ENTERED AT 10:33:07 ON 22 FEB 2001
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STRUCTURE FILE UPDATES: 20 FEB 2001 HIGHEST RN 322637-11-6
DICTIONARY FILE UPDATES: 20 FEB 2001 HIGHEST RN 322637-11-6

TSCA INFORMATION NOW CURRENT THROUGH July 8, 2000

Please note that search-term pricing does apply when
conducting SmartSELECT searches.

Structure search limits have been increased. See HELP SLIMIT
for details.

=> d que 11;d 11

L1 1 SEA FILE=REGISTRY ABB=ON "NITRIC OXIDE"/CN

L1 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2001 ACS
RN 10102-43-9 REGISTRY
CN Nitrogen oxide (NO) (8CI, 9CI) (CA INDEX NAME)
OTHER NAMES:
CN Amidogen, oxo-
CN **Nitric oxide**
CN Nitric oxide (NO)
CN Nitric oxide trimer
CN Nitrogen monooxide
CN Nitrogen monoxide
CN Nitrogen oxide (N4O4)
CN Nitrogen(II) oxide
CN Nitrosyl radical
DR 53851-19-7, 51005-20-0, 51005-21-1, 90452-29-2
MF N O
CI COM
LC STN Files: AGRICOLA, AIDSLINE, ANABSTR, APILIT, APILIT2, APIPAT,
APIPAT2, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CABA, CANCERLIT, CAPLUS,
CASREACT, CBNB, CEN, CHEMCATS, CHEMINFORMRX, CHEMLIST, CHEMSAFE, CIN,
CSCHEM, CSNB, DDFU, DETHERM*, DIPPR*, DRUGU, DRUGUPDATES, EMBASE,
GMELIN*, HSDB*, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MRCK*, MSDS-OHS,
NIOSHTIC, PDLCOM*, PIRA, PROMT, RTECS*, SPECINFO, TOXLINE, TOXLIT,
TRCTHERMO*, TULSA, ULIDAT, USPATFULL, VETU, VTB
(*File contains numerically searchable property data)
Other Sources: DSL**, EINECS**, TSCA**
(**Enter CHEMLIST File for up-to-date regulatory information)

N=O

56543 REFERENCES IN FILE CA (1967 TO DATE)
368 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
56698 REFERENCES IN FILE CAPLUS (1967 TO DATE)

=> d que 12;d 12

L2 1 SEA FILE=REGISTRY ABB=ON "NITRIC OXIDE SYNTHASE"/CN

L2 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2001 ACS
RN 125978-95-2 REGISTRY
CN Synthase, nitric oxide (9CI) (CA INDEX NAME)
OTHER NAMES:
CN Endothelium-derived relaxation factor-forming enzyme
CN Endothelium-derived relaxing factor synthase
CN **Nitric oxide synthase**
CN Nitric oxide synthetase
CN NO synthase
MF Unspecified
CI MAN
SR CA
LC STN Files: AGRICOLA, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CAPLUS, CEN,
CHEMCATS, CIN, CSCHEM, EMBASE, IPA, PROMT, TOXLINE, TOXLIT, USPATFULL

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
12089 REFERENCES IN FILE CA (1967 TO DATE)
40 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
12149 REFERENCES IN FILE CAPLUS (1967 TO DATE)

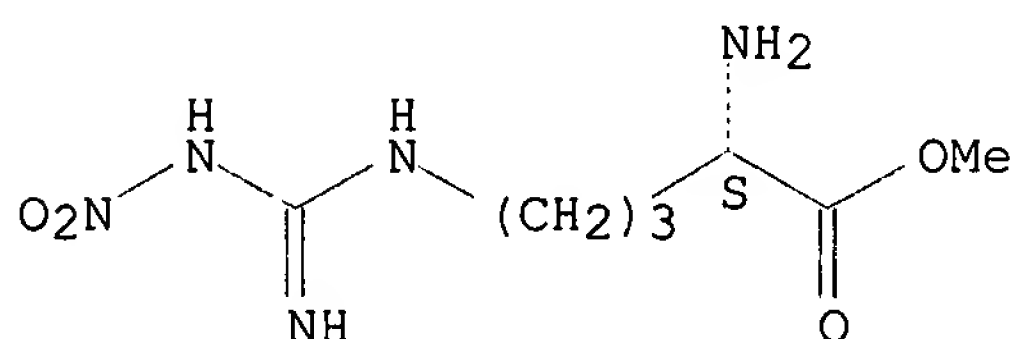
=> d que 112;d 112 1-2

L12 2 SEA FILE=REGISTRY ABB=ON 50903-99-6 OR 17035-90-4

L12 ANSWER 1 OF 2 REGISTRY COPYRIGHT 2001 ACS
RN 50903-99-6 REGISTRY
CN L-Ornithine, N5-[imino(nitroamino)methyl]-, methyl ester (9CI) (CA INDEX NAME)
OTHER NAMES:
CN L-NAME
CN L-NAME
CN N-Nitro-L-arginine methyl ester
CN N.omega.-Nitro-L-arginine methyl ester
CN N.omega.-Nitro-L-arginine methyl ester
CN NAME
CN NG-Nitro-L-arginine Me ester
CN NG-Nitro-L-arginine methyl ester
FS STEREOSEARCH
DR 162715-84-6, 126265-24-5, 189639-12-1
MF C7 H15 N5 O4
CI COM

LC STN Files: ADISINSIGHT, AGRICOLA, AIDSLINE, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAPLUS, CASREACT, CEN, CHEMCATS, CIN, DIOGENES, EMBASE, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, PROMT, RTECS*, TOXLINE, TOXLIT, USPATFULL
(*File contains numerically searchable property data)

Absolute stereochemistry.

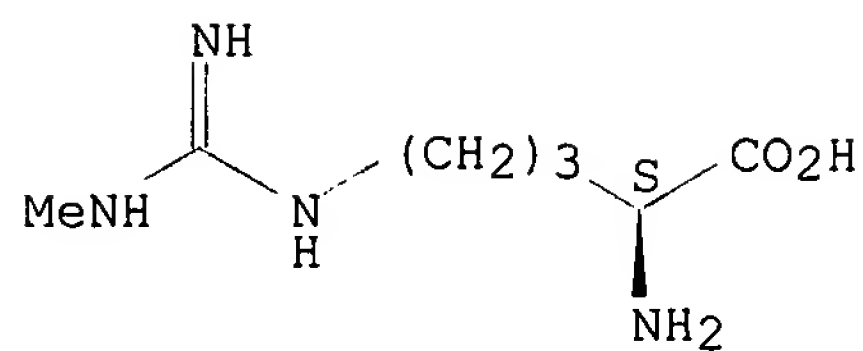


1086 REFERENCES IN FILE CA (1967 TO DATE)
5 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
1089 REFERENCES IN FILE CAPLUS (1967 TO DATE)

L12 ANSWER 2 OF 2 REGISTRY COPYRIGHT 2001 ACS
RN 17035-90-4 REGISTRY
CN L-Ornithine, N5-[imino(methylamino)methyl]- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Ornithine, N5-(methyamidino)-, L- (8CI)
OTHER NAMES:
CN .omega.-N-Methylarginine
CN .omega.-N-Monomethylarginine
CN L-NG-Methylarginine
CN L-NMA
CN L-NMMA
CN Methylarginine
CN N5-(Methyamidino)-L-ornithine
CN NG-Methyl-L-arginine
CN NG-Methylarginine
CN NG-Monomethyl-L-arginine
CN NG-Monomethylarginine
CN Targinine
FS STEREOSEARCH
DR 42342-68-7
MF C7 H16 N4 O2
CI COM
LC STN Files: ADISINSIGHT, AGRICOLA, AIDSLINE, BEILSTEIN*, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAPLUS, CASREACT, CHEMCATS, CHEMINFORMRX, CIN, CSCHEM, DDFU, DRUGPAT, DRUGU, DRUGUPDATES, EMBASE, IPA, MEDLINE, PROMT, SYNTHLINE, TOXLINE, TOXLIT, USPATFULL
(*File contains numerically searchable property data)

Absolute stereochemistry.

Prasad 09/395,038



718 REFERENCES IN FILE CA (1967 TO DATE)
3 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
718 REFERENCES IN FILE CAPLUS (1967 TO DATE)

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DEL HIS Y

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E NITRIC OXIDE/CN

L1 1 S E3
E NITRIC OXIDE SYTHETASE/CN
E NITRIC OXIDE SYNTHASE
E NITRIC OXIDE SYNTHASE/CN
L2 1 S E3

FILE 'HCAPLUS' ENTERED AT 10:20:53 ON 22 FEB 2001

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L7 9442 S IMMUNOSTIM?
L8 84 S L6 AND L7
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L14 875 S L NAME OR L NMMA
L15 1774 S L13 OR L14
L16 0 S L6 AND L15
L17 2 S L3 AND L14
L18 25593 S VACCINE#
L19 441 S L3 AND L18
L20 12 S L19 AND L5
L21 1 S L19 AND L14
L22 15 S L9 OR L10 OR L11 OR L17 OR L21 OR L20
L23 3172 S IMMUN? (3A) STIMUL?
L24 58 S L3 AND L23
L25 3 S L24 AND (L14 OR L5)
L26 16 S L25 OR L22

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L31 705 S (INTERLEUKIN 12 OR IL12 OR IL 12)
L32 130 S (INTERLEUKIN 12 OR IL12 OR IL 12)/CLM
L33 9 S L32 AND L30
L34 136 S (INTERLEUKIN 12 OR IL12 OR IL 12)/CLM, TI, AB
L35 9 S L34 AND (L29 OR L30)
L36 9 S L33 OR L35

FILE 'USPATFULL, HCAPLUS' ENTERED AT 10:32:18 ON 22 FEB 2001
L37 25 DUP REM L36 L26 (0 DUPLICATES REMOVED)

FILE 'REGISTRY' ENTERED AT 10:33:07 ON 22 FEB 2001

=> fil uspatfull hcaplus

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=> d bib ab it 1-25

L37 ANSWER 1 OF 25 USPATFULL

AN 2000:70440 USPATFULL

TI Enhanced activation of natural killer cells using an NK cell activator
and a hydrogen peroxide scavenger or inhibitor

IN Hellstrand, Jan Urban Kristoffer, Gothenburg, Sweden

Hermodsson, Svante Hermod, Molndal, Sweden

PA Maxim Pharmaceuticals, Inc., San Diego, CA, United States (U.S.
corporation)

PI US 6071509 20000606

AI US 1996-681108 19960722 (8)

RLI Continuation of Ser. No. US 1994-287200, filed on 8 Aug 1994, now
abandoned

DT Utility

EXNAM Primary Examiner: Celsa, Bennett; Assistant Examiner: Garcia, Maurie

LREP Knobbe, Martens, Olson & Bear, LLP

CLMN Number of Claims: 16

ECL Exemplary Claim: 1

DRWN 10 Drawing Figure(s); 10 Drawing Page(s)

LN.CNT 1174

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB An improved method for the prevention of the inactivation of natural
killer (NK) cells and the enhanced activation of NK cells in the
presence of monocytes using a combination of a natural killer cell
activator and a compound effective to inhibit the production or release
of intracellular hydrogen peroxide, or a hydrogen peroxide scavenger,

is

disclosed. The method is useful, for example, in the treatment of solid
tumors, metastases and viral infection.

IT Monocyte

(histamine augmentation of natural killer cell cytotoxicity against
tumor cells in presence of)

IT Neoplasm inhibitors

(interleukin-2 and histamine or H2-receptor agonist as)

IT Pharmaceutical dosage forms

(of interleukin-2 and histamine or H2-receptor agonist, for tumor
growth and metastasis inhibition)

IT Neurotransmitter agonists

(histaminic H2, interleukin-2 and tumor growth and metastasis
inhibition with)

IT Lymphokines and Cytokines
(interleukin 2, histamine or H2-receptor agonist and, tumor growth and metastasis inhibition with)

IT Neoplasm inhibitors
(metastasis, interleukin-2 and histamine or H2-receptor agonist as)

IT Lung, neoplasm
(metastasis, prevention of, with histamine and interleukin-2)

IT Lymphocyte
(natural killer, cytotoxicity of, against tumor cells, histamine and/or interleukin-2 effect on)

IT 51-45-6, Histamine, biological studies 51-45-6D, Histamine, analogs
(interleukin-2 and, tumor growth and metastasis inhibition with)

IT 65119-89-3, Dimaprit
(lung metastasis inhibition with)

IT 136218-98-9
(tumor growth and metastasis inhibition with)

L37 ANSWER 2 OF 25 USPATFULL

AN 2000:61190 USPATFULL

TI Enhanced activation of NK cells using an NK cell activator and a hydrogen peroxide scavenger or inhibitor

IN Hellstrand, Jan Urban Kristoffer, Goteborg, Sweden
Hermodsson, Svante Hermod, Molndal, Sweden

PA Maxim Pharmaceuticals, Inc., San Diego, CA, United States (U.S. corporation)

PI US 6063373 20000516

AI US 1997-932406 19970917 (8)

RLI Continuation of Ser. No. US 1996-602514, filed on 20 Feb 1996, now abandoned which is a division of Ser. No. US 1994-287200, filed on 8 Aug 1994, now abandoned which is a continuation-in-part of Ser. No. US 1992-843052, filed on 2 Mar 1992, now patented, Pat. No. US 5348739 which is a continuation-in-part of Ser. No. US 1989-409357, filed on 19 Sep 1989, now abandoned

DT Utility

EXNAM Primary Examiner: Celsa, Bennett; Assistant Examiner: Garcia, Maurie

LREP Knobbe, Martens, Olson & Bear, LLP

CLMN Number of Claims: 5

ECL Exemplary Claim: 1

DRWN 7 Drawing Figure(s); 10 Drawing Page(s)

LN.CNT 1097

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB An improved method for the prevention of the inactivation of natural killer (NK) cells and the enhanced activation of NK cells in the presence of monocytes using a combination of a natural killer cell activator and a compound effective to inhibit the production or release of intracellular hydrogen peroxide, or a hydrogen peroxide scavenger, is disclosed. The method is useful, for example, in the treatment of solid tumors, metastases and viral infection.

IT Monocyte
(histamine augmentation of natural killer cell cytotoxicity against tumor cells in presence of)

IT Neoplasm inhibitors
(interleukin-2 and histamine or H2-receptor agonist as)

IT Pharmaceutical dosage forms

(of interleukin-2 and histamine or H2-receptor agonist, for tumor growth and metastasis inhibition)

IT Neurotransmitter agonists
(histaminic H2, interleukin-2 and tumor growth and metastasis inhibition with)

IT Lymphokines and Cytokines
(interleukin 2, histamine or H2-receptor agonist and, tumor growth and metastasis inhibition with)

IT Neoplasm inhibitors
(metastasis, interleukin-2 and histamine or H2-receptor agonist as)

IT Lung, neoplasm
(metastasis, prevention of, with histamine and interleukin-2)

IT Lymphocyte
(natural killer, cytotoxicity of, against tumor cells, histamine and/or interleukin-2 effect on)

IT 51-45-6, Histamine, biological studies 51-45-6D, Histamine, analogs
(interleukin-2 and, tumor growth and metastasis inhibition with)

IT 65119-89-3, Dimaprit
(lung metastasis inhibition with)

IT 136218-98-9
(tumor growth and metastasis inhibition with)

L37 ANSWER 3 OF 25 USPATFULL

AN 2000:27800 USPATFULL

TI Recombinant swinepox virus

IN Cochran, Mark D., Carlsbad, CA, United States

Junker, David E., San Diego, CA, United States

PA Syntro Corporation, Lenexa, KS, United States (U.S. corporation)

PI US 6033904 20000307

AI US 1995-480640 19950607 (8)

RLI Continuation-in-part of Ser. No. US 1995-375922, filed on 19 Jan 1995 which is a continuation-in-part of Ser. No. WO 1994-US8277, filed on 22 Jul 1994 which is a continuation-in-part of Ser. No. US 1993-97554, filed on 22 Jul 1993, now patented, Pat. No. US 5869312 And a continuation-in-part of Ser. No. US 1992-820154, filed on 13 Jan 1992, now patented, Pat. No. US 5382425, issued on 17 Jan 1995

DT Utility

EXNAM Primary Examiner: Mosher, Mary E.; Assistant Examiner: Salini, Ali R

LREP White, John P. Copper & Dunham LLP

CLMN Number of Claims: 32

ECL Exemplary Claim: 1,7

DRWN 114 Drawing Figure(s); 114 Drawing Page(s)

LN.CNT 8999

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB This invention provides a recombinant swinepox virus comprising a foreign DNA sequence inserted into the swinepox virus genomic DNA, wherein the foreign DNA sequence is inserted within a HindIII N fragment

of the swinepox virus genomic DNA and is capable of being expressed in a swinepox virus infected host cell. The invention further provides homology vectors, vaccines and methods of immunization.

IT Glycoproteins, specific or class
(A, viral; recombinant swinepox virus for expression of foreign antigens in vaccine prepns.)

IT Glycoproteins, specific or class

(B, viral; recombinant swinepox virus for expression of foreign antigens in vaccine prepns.)

IT Glycoproteins, specific or class
(C, viral; recombinant swinepox virus for expression of foreign antigens in vaccine prepns.)

IT Glycoproteins, specific or class
(E, viral; recombinant swinepox virus for expression of foreign antigens in vaccine prepns.)

IT Glycoproteins, specific or class
(E1, viral; recombinant swinepox virus for expression of foreign antigens in vaccine prepns.)

IT Glycoproteins, specific or class
(E2, viral; recombinant swinepox virus for expression of foreign antigens in vaccine prepns.)

IT Proteins, specific or class
(F, viral; recombinant swinepox virus for expression of foreign antigens in vaccine prepns.)

IT Glycoproteins, specific or class
(G, viral; recombinant swinepox virus for expression of foreign antigens in vaccine prepns.)

IT Gene, microbial
(I4L, foreign DNA insertion into; recombinant swinepox virus for expression of foreign antigens in vaccine prepns.)

IT Gene, microbial
(I7L, foreign DNA insertion into; recombinant swinepox virus for expression of foreign antigens in vaccine prepns.)

IT Proteins, specific or class
(M (matrix), viral; recombinant swinepox virus for expression of foreign antigens in vaccine prepns.)

IT Proteins, specific or class
(N (nucleocapsid), viral; recombinant swinepox virus for expression of foreign antigens in vaccine prepns.)

IT Proteins, specific or class
(NP (nucleoprotein), viral; recombinant swinepox virus for expression of foreign antigens in vaccine prepns.)

IT Proteins, specific or class
(ORF 7, viral; recombinant swinepox virus for expression of foreign antigens in vaccine prepns.)

IT Proteins, specific or class
(VP2, viral; recombinant swinepox virus for expression of foreign antigens in vaccine prepns.)

IT Proteins, specific or class
(VP3, viral; recombinant swinepox virus for expression of foreign antigens in vaccine prepns.)

IT Lipoproteins
(VP4, viral; recombinant swinepox virus for expression of foreign antigens in vaccine prepns.)

IT Avian infectious bronchitis virus

IT Bovine diarrhea virus

IT Bovine herpesvirus 1

IT Bovine parainfluenza virus 3

IT Bovine respiratory syncytial virus

IT Chicken anemia virus

IT Equid herpesvirus 1

IT Equine influenza virus

IT Feline immunodeficiency virus

IT Gallid herpesvirus

IT Gallid herpesvirus 1
 IT Hepatitis B virus
 IT Hepatitis C virus
 IT Hog cholera virus
 IT Human herpesvirus
 IT Human herpesvirus 1
 IT Human herpesvirus 2
 IT Human herpesvirus 3
 IT Human herpesvirus 4
 IT Human herpesvirus 5
 IT Human herpesvirus 6
 IT Human herpesvirus 7
 IT Human immunodeficiency virus
 IT Infectious bursal disease virus
 IT Influenza virus
 IT Measles virus
 IT Newcastle disease virus
 IT Pseudorabies virus
 IT Pseudorabies virus 3
 IT Rabies virus
 IT Swine infertility and respiratory syndrome virus
 IT Swine influenza virus
 (antigens from; recombinant swinepox virus for expression of foreign
 antigens in vaccine prepns.)
 IT Proteins, specific or class
 (attachment, viral; recombinant swinepox virus for expression of
 foreign antigens in vaccine prepns.)
 IT Glycoproteins, specific or class
 (gpD, viral; recombinant swinepox virus for expression of foreign
 antigens in vaccine prepns.)
 IT Glycoproteins, specific or class
 (gpE, viral; recombinant swinepox virus for expression of foreign
 antigens in vaccine prepns.)
 IT Glycoproteins, specific or class
 (gpH, viral; recombinant swinepox virus for expression of foreign
 antigens in vaccine prepns.)
 IT Glycoproteins, specific or class
 (gpI, viral; recombinant swinepox virus for expression of foreign
 antigens in vaccine prepns.)
 IT Glycoproteins, specific or class
 (gp48, viral; recombinant swinepox virus for expression of foreign
 antigens in vaccine prepns.)
 IT Glycoproteins, specific or class
 (gp50, viral; recombinant swinepox virus for expression of foreign
 antigens in vaccine prepns.)
 IT Glycoproteins, specific or class
 (gp53, viral; recombinant swinepox virus for expression of foreign
 antigens in vaccine prepns.)
 IT Antigens
 (hepatitis B core; recombinant swinepox virus for expression of
 foreign
 antigens in vaccine prepns.)
 IT Antigens
 (hepatitis B surface; recombinant swinepox virus for expression of
 foreign antigens in vaccine prepns.)
 IT Plasmid vectors
 (homol. vectors; recombinant swinepox virus for expression of foreign

antigens in vaccine prepns.)

IT Hemopoietins
(myelomonocytic growth factors, chicken; recombinant swinepox virus
for expression of foreign antigens in vaccine prepns.)

IT Swinepox virus

IT Virus vectors
(recombinant swinepox virus for expression of foreign antigens in
vaccine prepns.)

IT Promoter (genetic element)
(recombinant swinepox virus for expression of foreign antigens in
vaccine prepns.)

IT Antigens
(recombinant swinepox virus for expression of foreign antigens in
vaccine prepns.)

IT Cytokines
(recombinant swinepox virus for expression of foreign antigens in
vaccine prepns.)

IT Hemagglutinins
(recombinant swinepox virus for expression of foreign antigens in
vaccine prepns.)

IT Interferons
(recombinant swinepox virus for expression of foreign antigens in
vaccine prepns.)

IT Interleukin 12
(recombinant swinepox virus for expression of foreign antigens in
vaccine prepns.)

IT Interleukin 2
(recombinant swinepox virus for expression of foreign antigens in
vaccine prepns.)

IT Interleukin 6
(recombinant swinepox virus for expression of foreign antigens in
vaccine prepns.)

IT Interleukin receptors
(recombinant swinepox virus for expression of foreign antigens in
vaccine prepns.)

IT Glycoproteins, specific or class
(spike, viral; recombinant swinepox virus for expression of foreign
antigens in vaccine prepns.)

IT Vaccines
(synthetic; recombinant swinepox virus for expression of foreign
antigens in vaccine prepns.)

IT Envelope proteins

IT Polyproteins

IT gag proteins
(viral; recombinant swinepox virus for expression of foreign antigens
in vaccine prepns.)

IT 9001-45-0, .beta.-Glucuronidase 9031-11-2, .beta.-Galactosidase
(Escherichia coli; recombinant swinepox virus for expression of
foreign antigens in vaccine prepns.)

IT 9001-67-6, Neuraminidase 83869-56-1, GM-CSF
(recombinant swinepox virus for expression of foreign antigens in
vaccine prepns.)

IT 150549-26-1 150549-27-2 150549-28-3 158969-89-2 222351-61-3
222351-62-4 222351-63-5 222351-64-6 222351-65-7 222652-83-7
222652-84-8 222652-85-9 222652-86-0 222652-87-1 222652-88-2

222652-89-3 222652-90-6 222652-91-7 222652-92-8 222652-93-9
 222652-94-0 243925-27-1, 7: PN: US6033904 SEQID: 9 unclaimed DNA
 243925-28-2, 8: PN: US6033904 SEQID: 10 unclaimed DNA 243925-29-3, 9:
 PN: US6033904 SEQID: 13 unclaimed DNA 243925-30-6 243925-31-7
 243925-32-8 243925-33-9 243925-34-0 243925-35-1 243925-36-2
 243925-37-3 243925-38-4 243925-39-5 243925-40-8 243925-41-9
 243925-42-0 243925-43-1 243925-44-2 243925-45-3 243925-46-4
 243925-47-5 243925-48-6 243925-49-7 243925-50-0 243925-51-1
 243925-52-2 243925-53-3 243925-54-4 243925-56-6 243925-59-9
 243925-62-4 243925-63-5 243925-64-6 243925-65-7 243925-66-8
 243925-67-9 243925-68-0 243925-69-1 243925-70-4 243925-71-5
 243925-72-6 260238-94-6 260238-95-7 260238-96-8 260238-97-9
 260238-98-0 260238-99-1 260239-02-9 260239-03-0 260239-04-1
 260239-05-2 260239-06-3 260239-07-4 260239-08-5 260239-09-6
 260239-10-9 260239-11-0 260239-12-1 260239-13-2 260239-14-3
 260239-15-4 260239-16-5 260239-17-6 260239-18-7 260239-19-8
 260239-20-1 260239-21-2 260239-22-3 260239-23-4 260239-24-5
 260239-25-6 260239-26-7 260239-27-8 260239-28-9 260239-29-0
 260239-30-3 260239-31-4 260239-32-5 260239-33-6 260239-34-7
 260239-38-1 260239-40-5 260239-41-6 260239-42-7 260239-43-8
 260239-44-9 260239-45-0 260239-46-1 260239-47-2 260239-48-3
 260239-49-4 260239-50-7 260239-51-8 260239-52-9 260239-53-0
 260239-54-1 260239-55-2 260239-56-3 260239-57-4 260239-58-5
 260239-59-6 260239-60-9 260239-61-0

(unclaimed nucleotide sequence; recombinant swinepox virus for expression of foreign antigens in vaccine preps.)

IT 177698-75-8 260238-89-9 260238-90-2 260238-91-3 260238-92-4
 260238-93-5 260239-00-7 260239-01-8 260239-35-8 260239-36-9
 260239-37-0 260239-39-2 260365-27-3

(unclaimed protein sequence; recombinant swinepox virus for expression of foreign antigens in vaccine preps.)

IT 72-18-4, L-Valine, properties 2640-07-5 42155-95-3 260052-07-1
 260052-08-2 260052-09-3 260052-10-6 260052-11-7 260052-12-8
 260052-13-9 260052-14-0 260052-15-1 260052-16-2 260052-17-3
 260052-18-4 260052-19-5 260052-20-8 260052-21-9 260052-22-0
 260052-23-1 260052-24-2

(unclaimed sequence; recombinant swinepox virus for expression of foreign antigens in vaccine preps.)

L37 ANSWER 4 OF 25 HCAPLUS COPYRIGHT 2001 ACS

AN 2000:240985 HCAPLUS

DN 132:292701

TI Novel methods for therapeutic vaccination ✓

IN Steinaa, Lucilla; Mouritsen, Soren; Nielsen, Klaus Gregorious; Haaning, Jesper; Leach, Dana; Dalum, Iben; Gautam, Anand; Birk, Peter; Karlsson, Gunilla

PA M Amp E Biotech A/s, Den.

SO PCT Int. Appl., 220 pp.

CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2000020027	A2	20000413	WO 1999-DK525	19991005

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L37 ANSWER 4 OF 25 HCAPLUS COPYRIGHT 2001 ACS

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	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2000020027	A2	20000413	WO 1999-DK525	19991005
	WO 2000020027	A3	20001012		

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRAI DK 1998-1261 19981005

US 1998-105011 19981020

AB A method is disclosed for inducing cell-mediated immunity against cellular

antigens. More specifically, the invention provides for a method for inducing cytotoxic T-lymphocyte immunity against weak antigens, notably self-proteins. The method entails that antigen presenting cells are induced to present at least one CTL epitope of the weak antigen and at

the

same time presenting at least one foreign T-helper lymphocyte epitope.

In

a preferred embodiment, the antigen is a cancer specific antigen, e.g. prostate specific membrane antigen (PSM), Her2, or FGF8b. The method can be exercised by using traditional polypeptide vaccination, but also by using live attenuated vaccines or nucleic acid vaccination. The

invention

furthermore provides immunogenic analogs of PSM, Her2 and FGF8b, as well as nucleic acid mols. encoding these analogs. Also vectors and transformed cells are disclosed. The invention also provides for a

method

for identification of immunogenic analogs of weak or non-immunogenic antigens.

IC A61K039-00

CC 15-2 (Immunochemistry)

Section cross-reference(s): 3, 63

ST weak antigen **vaccine** cytotoxic T lymphocyte; tumor antigen T cell epitope **vaccine**

IT Antigens

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (17-1A; weak antigens inserted with foreign T cell epitope as
vaccines)

IT Antigens
 RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL
 (Biological study); USES (Uses)
 (AM-1; weak antigens inserted with foreign T cell epitope as
vaccines)

IT Antigens
 RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL
 (Biological study); USES (Uses)
 (APC; weak antigens inserted with foreign T cell epitope as
vaccines)

IT Antigens
 RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL
 (Biological study); USES (Uses)
 (APRIL; weak antigens inserted with foreign T cell epitope as
vaccines)

IT Antigens
 RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL
 (Biological study); USES (Uses)
 (BAGE; weak antigens inserted with foreign T cell epitope as
vaccines)

IT Chemokines
 (C-X-C, Ena78; weak antigens inserted with foreign T cell epitope as
vaccines)

IT CD antigens
 RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL
 (Biological study); USES (Uses)
 (CD33; weak antigens inserted with foreign T cell epitope as
vaccines)

IT Glycoproteins, specific or class
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (CD40-L (antigen CD40 ligand); weak antigens inserted with foreign T
 cell epitope as **vaccines**)

IT Antigens
 RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL
 (Biological study); USES (Uses)
 (CD52; weak antigens inserted with foreign T cell epitope as
vaccines)

IT Antigens
 RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL
 (Biological study); USES (Uses)
 (CDC27; weak antigens inserted with foreign T cell epitope as
vaccines)

IT Antigens
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (CO17-1A; weak antigens inserted with foreign T cell epitope as
vaccines)

IT Antigens
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (CS (circumsporozoite), epitope; weak antigens inserted with foreign T
 cell epitope as **vaccines**)

IT Proteins, specific or class
 RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL
 (Biological study); USES (Uses)
 (DCC (deleted in colorectal cancer); weak antigens inserted with

foreign T cell epitope as **vaccines**)

IT Antigens
 RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (DcR3; weak antigens inserted with foreign T cell epitope as **vaccines**)

IT Proteins, specific or class
 RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (E6; weak antigens inserted with foreign T cell epitope as **vaccines**)

IT Transcription factors
 RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (E7; weak antigens inserted with foreign T cell epitope as **vaccines**)

IT Hematopoietin receptors
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (FLT3 receptors; weak antigens inserted with foreign T cell epitope as **vaccines**)

IT Glycoproteins, specific or class
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (GP1; weak antigens inserted with foreign T cell epitope as **vaccines**)

IT Proteins, specific or class
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (H-ras; weak antigens inserted with foreign T cell epitope as **vaccines**)

IT Antigens
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (HMTV; weak antigens inserted with foreign T cell epitope as **vaccines**)

IT Heat-shock proteins
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (HSP 70; weak antigens inserted with foreign T cell epitope as **vaccines**)

IT Heat-shock proteins
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (HSP 90; weak antigens inserted with foreign T cell epitope as **vaccines**)

IT Immunoglobulin receptors
 RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (IgE type II; weak antigens inserted with foreign T cell epitope as **vaccines**)

IT Proteins, specific or class
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (K-ras; weak antigens inserted with foreign T cell epitope as **vaccines**)

IT Lipoprotein receptors
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (LDL, fusion with FUT or fucosyltransferase; weak antigens inserted with foreign T cell epitope as **vaccines**)

IT Glycoproteins, specific or class
 RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (MCP (membrane cofactor protein); weak antigens inserted with foreign

- cell epitope as **vaccines**)

IT Multidrug resistance proteins
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (MDR1; weak antigens inserted with foreign T cell epitope as
vaccines)
- IT Histocompatibility antigens
 RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL
 (Biological study); PROC (Process)
 (MHC (major histocompatibility complex), class I; weak antigens
 inserted with foreign T cell epitope as **vaccines**)
- IT Histocompatibility antigens
 RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL
 (Biological study); PROC (Process)
 (MHC (major histocompatibility complex), class II; weak antigens
 inserted with foreign T cell epitope as **vaccines**)
- IT Diglycerides
 RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL
 (Biological study); USES (Uses)
 (N-acyl; weak antigens inserted with foreign T cell epitope as
vaccines)
- IT Proteins, specific or class
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (N-ras; weak antigens inserted with foreign T cell epitope as
vaccines)
- IT Glycoproteins, specific or class
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (P170; weak antigens inserted with foreign T cell epitope as
vaccines)
- IT Phosphoproteins
 RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL
 (Biological study); USES (Uses)
 (P210bcr-c-abl; weak antigens inserted with foreign T cell epitope as
vaccines)
- IT Prostate-specific antigen
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (PSA and PSM; weak antigens inserted with foreign T cell epitope as
vaccines)
- IT Hemopoietins
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (Progenipoietin; weak antigens inserted with foreign T cell epitope as
vaccines)
- IT Transcription factors
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (Rb; weak antigens inserted with foreign T cell epitope as
vaccines)
- IT Antigens
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (SART-1; weak antigens inserted with foreign T cell epitope as
vaccines)
- IT Gene, animal
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (SSX; weak antigens inserted with foreign T cell epitope as
vaccines)
- IT Transcription factors
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (STAT3; weak antigens inserted with foreign T cell epitope as
vaccines)

IT Mucins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(STn antigen; weak antigens inserted with foreign T cell epitope as **vaccines**)

IT Antigens
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(TAG-72 (tumor-assocd. glycoprotein 72); weak antigens inserted with foreign T cell epitope as **vaccines**)

IT Antigens
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(TPA (tissue protein antigen); weak antigens inserted with foreign T cell epitope as **vaccines**)

IT Proteins, specific or class
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(TRP-1 (tyrosinase-related protein 1); weak antigens inserted with foreign T cell epitope as **vaccines**)

IT Proteins, specific or class
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(TRP-2 (tyrosinase-related protein 2); weak antigens inserted with foreign T cell epitope as **vaccines**)

IT Polyoxyalkylenes, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**adjuvant**; weak antigens inserted with foreign T cell epitope as **vaccines**)

IT Immunostimulants
(**adjuvants**, Freund's incomplete; weak antigens inserted with foreign T cell epitope as **vaccines**)

IT Immunostimulants
(**adjuvants**, Freund's; weak antigens inserted with foreign T cell epitope as **vaccines**)

IT Immunostimulants
(**adjuvants**, ISCOMs; weak antigens inserted with foreign T cell epitope as **vaccines**)

IT Immunostimulants
(**adjuvants**, Ribi; weak antigens inserted with foreign T cell epitope as **vaccines**)

IT Immunostimulants
(**adjuvants**; weak antigens inserted with foreign T cell epitope as **vaccines**)

IT Drug delivery systems
(anal; weak antigens inserted with foreign T cell epitope as **vaccines**)

IT Animal virus
Bacteria (Eubacteria)
Parasite
(antigen; weak antigens inserted with foreign T cell epitope as **vaccines**)

IT Proteins, specific or class
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(bcl-2; weak antigens inserted with foreign T cell epitope as **vaccines**)

IT Drug delivery systems
(buccal; weak antigens inserted with foreign T cell epitope as **vaccines**)

IT Transcription factors
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL

(Biological study); USES (Uses)
(c-myc; weak antigens inserted with foreign T cell epitope as
vaccines)

IT Diagnosis
(cancer; weak antigens inserted with foreign T cell epitope as
vaccines)

IT T cell (lymphocyte)
(cytotoxic, epitope; weak antigens inserted with foreign T cell
epitope
as **vaccines**)

IT Mutation
(deletion; weak antigens inserted with foreign T cell epitope as
vaccines)

IT Neoplasm
(diagnosis; weak antigens inserted with foreign T cell epitope as
vaccines)

IT Toxoids
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(diphtheria, epitope; weak antigens inserted with foreign T cell
epitope as **vaccines**)

IT Glycophosphoproteins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(endoplasmins; weak antigens inserted with foreign T cell epitope as
vaccines)

IT Toxins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(enterotoxins, heat-labile; weak antigens inserted with foreign T cell
epitope as **vaccines**)

IT Drug delivery systems
(epidural; weak antigens inserted with foreign T cell epitope as
vaccines)

IT Mucins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(episialins; weak antigens inserted with foreign T cell epitope as
vaccines)

IT B cell (lymphocyte)
T cell (lymphocyte)
(epitope; weak antigens inserted with foreign T cell epitope as
vaccines)

IT Hemagglutinins
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL
(Biological study); USES (Uses)
(epitope; weak antigens inserted with foreign T cell epitope as
vaccines)

IT Functional groups
(farnesyl; weak antigens inserted with foreign T cell epitope as
vaccines)

IT Receptors
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(folate; weak antigens inserted with foreign T cell epitope as
vaccines)

IT Immunoglobulins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(fragments; weak antigens inserted with foreign T cell epitope as
vaccines)

IT Vascular endothelial growth factor receptors
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL

(Biological study); USES (Uses)
 (gene KDR; weak antigens inserted with foreign T cell epitope as
vaccines)

IT Functional groups
 (geranyl-geranyl; weak antigens inserted with foreign T cell epitope
 as
vaccines)

IT Protein motifs
 (glycosylation site; weak antigens inserted with foreign T cell
 epitope
 as **vaccines**)

IT Glycoproteins, specific or class
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (gp100; weak antigens inserted with foreign T cell epitope as
vaccines)

IT Glycoproteins, specific or class
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (gp15; weak antigens inserted with foreign T cell epitope as
vaccines)

IT Sialoglycoproteins
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (gp75; weak antigens inserted with foreign T cell epitope as
vaccines)

IT T cell (lymphocyte)
 (helper cell, epitope; weak antigens inserted with foreign T cell
 epitope as **vaccines**)

IT Phosphoproteins
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (hsc 70 (heat-shock cognate, 70,000-mol.-wt.); weak antigens inserted
 with foreign T cell epitope as **vaccines**)

IT Drug delivery systems
 (injections, s.c.; weak antigens inserted with foreign T cell epitope
 as **vaccines**)

IT Mutation
 (insertion; weak antigens inserted with foreign T cell epitope as
vaccines)

IT Interleukin receptors
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (interleukin 13 receptors; weak antigens inserted with foreign T cell
 epitope as **vaccines**)

IT Drug delivery systems
 (intracranial; weak antigens inserted with foreign T cell epitope as
vaccines)

IT Drug delivery systems
 (intracutaneous; weak antigens inserted with foreign T cell epitope as
vaccines)

IT Drug delivery systems
 (intradermal; weak antigens inserted with foreign T cell epitope as
vaccines)

IT Hemolysins
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (listeriolysins; weak antigens inserted with foreign T cell epitope as
vaccines)

IT Proteins, specific or class
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (mammaglobin; weak antigens inserted with foreign T cell epitope as
vaccines)

IT Antigens
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (melanoma-assocd., MAGE; weak antigens inserted with foreign T cell
 epitope as **vaccines**)

IT Antigens
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (melanoma-assocd., Melan-A/MART-1; weak antigens inserted with foreign
 T cell epitope as **vaccines**)

IT Transferrins
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (melanotransferrins; weak antigens inserted with foreign T cell
 epitope
 as **vaccines**)

IT Chromosome
 (minichromosomes; weak antigens inserted with foreign T cell epitope
 as
vaccines)

IT Chemicals
 (modification; weak antigens inserted with foreign T cell epitope as
vaccines)

IT Mucins
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (mucin 2, 3 and 4; weak antigens inserted with foreign T cell epitope
 as **vaccines**)

IT Functional groups
 (myristyl; weak antigens inserted with foreign T cell epitope as
vaccines)

IT DNA
 RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL
 (Biological study); USES (Uses)
 (naked; weak antigens inserted with foreign T cell epitope as
vaccines)

IT Mammary gland
 Prostate gland
 (neoplasm; weak antigens inserted with foreign T cell epitope as
vaccines)

IT Microorganism
 (non-pathogenic; weak antigens inserted with foreign T cell epitope as
vaccines)

IT Liquids
 (oils formulation; weak antigens inserted with foreign T cell epitope
 as **vaccines**)

IT Drug delivery systems
 (oral; weak antigens inserted with foreign T cell epitope as
vaccines)

IT Proteins, specific or class
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (p15; weak antigens inserted with foreign T cell epitope as
vaccines)

IT Functional groups
 (palmitoyl; weak antigens inserted with foreign T cell epitope as
vaccines)

IT Drug delivery systems
 (parenterals; weak antigens inserted with foreign T cell epitope as
vaccines)

IT Drug delivery systems
 (peritoneal; weak antigens inserted with foreign T cell epitope as

vaccines)

IT Glycolipoproteins
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (phosphatidylinositol-contg.; weak antigens inserted with foreign T cell epitope as **vaccines)**

IT Proteins, specific or class
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (probasins; weak antigens inserted with foreign T cell epitope as **vaccines)**

IT Glycoproteins, specific or class
 RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (prostateins; weak antigens inserted with foreign T cell epitope as **vaccines)**

IT Interleukin 13
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (receptors; weak antigens inserted with foreign T cell epitope as **vaccines)**

IT Proteins, specific or class
 RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (self; weak antigens inserted with foreign T cell epitope as **vaccines)**

IT Drug delivery systems
 (spinal; weak antigens inserted with foreign T cell epitope as **vaccines)**

IT Drug delivery systems
 (subdermal; weak antigens inserted with foreign T cell epitope as **vaccines)**

IT Drug delivery systems
 (sublingual; weak antigens inserted with foreign T cell epitope as **vaccines)**

IT Mutation
 (substitution; weak antigens inserted with foreign T cell epitope as **vaccines)**

IT Antigens
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (surface; weak antigens inserted with foreign T cell epitope as **vaccines)**

IT Genetic element
 RL: BSU (Biological study, unclassified); BIOL (Biological study)
 (terminator; weak antigens inserted with foreign T cell epitope as **vaccines)**

IT Toxoids
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (tetanus, epitope; weak antigens inserted with foreign T cell epitope as **vaccines)**

IT Proteins, specific or class
 RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (transfection-facilitating; weak antigens inserted with foreign T cell epitope as **vaccines)**

IT Proteins, specific or class
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (transmembrane, mesothelin; weak antigens inserted with foreign T cell epitope as **vaccines)**

IT Antigens

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (tumor-assocd., G250; weak antigens inserted with foreign T cell
 epitope as **vaccines**)

IT Antigens
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (tumor-assocd., GAGE; weak antigens inserted with foreign T cell
 epitope as **vaccines**)

IT Antigens
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (tumor-assocd., KIAA0205 bladder carcinoma antigen; weak antigens
 inserted with foreign T cell epitope as **vaccines**)

IT Antigens
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (tumor-assocd., MAP17; weak antigens inserted with foreign T cell
 epitope as **vaccines**)

IT Antigens
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (tumor-assocd., MIC A/B; weak antigens inserted with foreign T cell
 epitope as **vaccines**)

IT Antigens
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (tumor-assocd., MUM-1; weak antigens inserted with foreign T cell
 epitope as **vaccines**)

IT Antigens
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (tumor-assocd., NY-ESO-1; weak antigens inserted with foreign T cell
 epitope as **vaccines**)

IT Antigens
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (tumor-assocd., PRAME; weak antigens inserted with foreign T cell
 epitope as **vaccines**)

IT Antigens
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (tumor-assocd., Pmel-17; weak antigens inserted with foreign T cell
 epitope as **vaccines**)

IT Antigens
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (tumor-assocd., RCAS1; weak antigens inserted with foreign T cell
 epitope as **vaccines**)

IT Antigens
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (tumor-assocd., ZAG; weak antigens inserted with foreign T cell
 epitope
 as **vaccines**)

IT Antigens
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (tumor-assocd., p16INK4; weak antigens inserted with foreign T cell
 epitope as **vaccines**)

IT Antigens
 RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL
 (Biological study); USES (Uses)
 (tumor-assocd.; weak antigens inserted with foreign T cell epitope as
vaccines)

IT Antigens
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (tumor-rejection, RAGE-1; weak antigens inserted with foreign T cell
 epitope as **vaccines**)

- IT Complement receptors
 RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (type 1; weak antigens inserted with foreign T cell epitope as **vaccines**)
- IT Complement receptors
 RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (type 2; weak antigens inserted with foreign T cell epitope as **vaccines**)
- IT Animal
 Animal cell line
 Antigen-presenting cell
 Antitumor agents
 Bacteriophage
 Carriers
 Cosmids
 DNA sequences
 Dendritic cell
 Encapsulation
 Epitopes
 Immunotherapy
 Influenza virus
 Latex
 Liposomes
 Macrophage
 Micelles
 Molecular cloning
 Mycobacterium
 Particles
 Plasmids
 Plasmodium falciparum
 Protein sequences
 Quillaja saponaria
Vaccines
 Virus
 Virus vectors
 (weak antigens inserted with foreign T cell epitope as **vaccines**)
- IT Gene, animal
 Promoter (genetic element)
 RL: BSU (Biological study, unclassified); BIOL (Biological study)
 (weak antigens inserted with foreign T cell epitope as **vaccines**)
- IT CA 125 (carbohydrate antigen)
 CD19 (antigen)
 CD20 (antigen)
 CD22 (antigen)
 CD44 (antigen)
 CD45 (antigen)
 CD5 (antigen)
 CD59 (antigen)
 Carcinoembryonic antigen
 Enzymes, biological studies
 Epidermal growth factor receptors
 Haptens
 .alpha.-Fetoproteins

RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (weak antigens inserted with foreign T cell epitope as **vaccines**)

IT Antibodies
 Antigens
 CD40 (antigen)
 CTLA-4 (antigen)
 Calreticulin
 Carbohydrates, biological studies
 Cytokines
 DNA
 Heat-shock proteins
 Insulin-like growth factor I receptors
 Interleukin 1
Interleukin 12
 Interleukin 13
 Interleukin 15
 Interleukin 2
 Interleukin 4
 Interleukin 6
 Ki-67 antigen
 Lipid A
 Lipids, biological studies
 Osteonectin
 Plastics, biological studies
 Platelet-derived growth factors
 Polymers, biological studies
 Receptors
 Saponins
 Toxins
 Tumor necrosis factors
 neu (receptor)
 p53 (protein)
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (weak antigens inserted with foreign T cell epitope as **vaccines**)

IT Transforming growth factors
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (.alpha.-; weak antigens inserted with foreign T cell epitope as **vaccines**)

IT Catenins
 RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (.beta.-; weak antigens inserted with foreign T cell epitope as **vaccines**)

IT Transforming growth factors
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (.beta.-; weak antigens inserted with foreign T cell epitope as **vaccines**)

IT Interferons
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (.gamma.-; weak antigens inserted with foreign T cell epitope as **vaccines**)

IT 39391-18-9
 RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(2; weak antigens inserted with foreign T cell epitope as
vaccines)

IT 62031-54-3, FGF
 RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL
 (Biological study); USES (Uses)
 (8a and 8b isoforms; weak antigens inserted with foreign T cell
 epitope
 as **vaccines**)

IT 264178-47-4P
 RL: BPN (Biosynthetic preparation); BSU (Biological study, unclassified);
 PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PREP
 (Preparation); USES (Uses)
 (P2 epitope gene; weak antigens inserted with foreign T cell epitope
 as
vaccines)

IT 126779-13-3P
 RL: BPN (Biosynthetic preparation); BSU (Biological study, unclassified);
 PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PREP
 (Preparation); USES (Uses)
 (P2 epitope; weak antigens inserted with foreign T cell epitope as
vaccines)

IT 264185-70-8P
 RL: BPN (Biosynthetic preparation); BSU (Biological study, unclassified);
 PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PREP
 (Preparation); USES (Uses)
 (P30 epitope gene; weak antigens inserted with foreign T cell epitope
 as **vaccines**)

IT 126779-14-4P
 RL: BPN (Biosynthetic preparation); BSU (Biological study, unclassified);
 PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PREP
 (Preparation); USES (Uses)
 (P30 epitope; weak antigens inserted with foreign T cell epitope as
vaccines)

IT 99-20-7D, Trehalose, diester 7429-90-5, Aluminum, biological studies
 9004-54-0, Dextran, biological studies 9005-25-8, Starch, biological
 studies 25322-68-3 53678-77-6, Muramyl dipeptide
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (**adjuvant**; weak antigens inserted with foreign T cell epitope
 as **vaccines**)

IT 148997-75-5, Androgen-induced growth factor (mouse clone pSC17 precursor
 reduced) 264179-58-0 264179-59-1, Neu (receptor) (human)
 264179-62-6
 264179-64-8 264179-65-9 264179-66-0 264179-67-1 264179-68-2
 RL: BSU (Biological study, unclassified); PRP (Properties); BIOL
 (Biological study)
 (amino acid sequence; weak antigens inserted with foreign T cell
 epitope as **vaccines**)

IT 3458-28-4, Mannose 9036-88-8, Mannan
 RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL
 (Biological study); PROC (Process)
 (binding partner; weak antigens inserted with foreign T cell epitope
 as
vaccines)

IT 56093-23-3
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (fusion with LDL receptor; weak antigens inserted with foreign T cell
 epitope as **vaccines**)

IT 125978-95-2, Nitric oxide synthase
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (inducible; weak antigens inserted with foreign T cell epitope as
vaccines)

IT 9030-23-3, Thymidine phosphorylase
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (inhibitor; weak antigens inserted with foreign T cell epitope as
vaccines)

IT 141907-41-7, Matrix metalloproteinase
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (isoforms; weak antigens inserted with foreign T cell epitope as
vaccines)

IT 100040-73-1, DNA (human clone .lambda.HER2-436 gene HER2 receptor cDNA)
 264179-57-9 264179-60-4 264179-61-5 264179-63-7
 RL: BSU (Biological study, unclassified); PRP (Properties); BIOL
 (Biological study)
 (nucleotide sequence; weak antigens inserted with foreign T cell
 epitope as **vaccines**)

IT 52-90-4, Cysteine, biological studies
 RL: BSU (Biological study, unclassified); BIOL (Biological study)
 (residue; weak antigens inserted with foreign T cell epitope as
vaccines)

IT 264134-70-5P 264134-71-6P 264134-72-7P 264134-73-8P 264134-78-3P
 264224-61-5P 264224-76-2P
 RL: BPN (Biosynthetic preparation); BSU (Biological study, unclassified);
 PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PREP
 (Preparation); USES (Uses)
 (weak antigens inserted with foreign T cell epitope as **vaccines**
)

IT 71965-46-3, Cathepsins 99085-47-9, Complement decay-accelerating factor
 147014-97-9, Cyclin-dependent kinase 4 179241-78-2, Caspase 8
 RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL
 (Biological study); USES (Uses)
 (weak antigens inserted with foreign T cell epitope as **vaccines**
)

IT 251541-10-3, Human Her2 protein (59-73) 251542-12-8, Human Her2 protein
 (465-479) 264617-99-4, Human PSM (87-108) 264618-03-3, Human PSM
 (210-230) 264618-06-6, Human PSM (269-289) 264618-07-7, Human PSM
 (298-324) 264618-08-8, Human PSM (442-465) 264618-09-9, Human PSM
 (488-514) 264618-23-7, Human PSM (598-630) 264619-18-3, Human PSM
 (643-662) 264619-84-3, Human PSM (672-699) 264620-57-7, Human Her2
 protein (5-25) 264620-84-0, Human Her2 protein (103-117) 264621-04-7,
 Human Her2 protein (149-163) 264621-94-5, Human Her2 protein (210-224)
 264622-06-2, Human Her2 protein (250-264) 264622-08-4, Human Her2
 protein (325-339) 264622-09-5, Human Her2 protein (369-383)
 264622-23-3, Human Her2 protein (579-593) 264624-69-3, Human Her2
 protein (632-652) 264624-79-5, Human Her2 protein (653-667)
 264624-80-8, Human Her2 protein (661-675) 264625-23-2, Human Her2
 protein (695-709) 264625-25-4, Human Her2 protein (72-86)
 264625-36-7,
 Human Her2 protein (146-160) 264625-37-8, Human Her2 protein (221-235)
 264625-38-9, Human Her2 protein (257-271) 264625-51-6, Human FGF8b
 protein (1-54) 264626-02-0, Human FGF8b protein (55-58) 264626-17-7,
 Human FGF8b protein (178-215) 264626-69-9, Human FGF8b protein (63-68)
 264626-82-6, Human FGF8b protein (72-76) 264626-84-8, Human FGF8b
 protein (85-91) 264626-85-9, Human FGF8b protein (95-102)
 264626-86-0,

Human FGF8b protein (106-111) 264626-87-1, Human FGF8b protein
(115-120)
264627-05-6, Human FGF8b protein (128-134) 264627-07-8, Human FGF8b
protein (138-144) 264627-09-0, Human FGF8b protein (149-154)
264627-10-3, Human FGF8b protein (158-162) 264627-11-4, Human FGF8b
protein (173-177) 264627-12-5, Human FGF8b protein (26-45)
RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study);
USES
(Uses)
(weak antigens inserted with foreign T cell epitope as **vaccines**
)
IT 3700-67-2 9001-91-6, Plasminogen 9002-10-2, Tyrosinase 9002-61-3,
Human chorionic gonadotropin 9032-22-8, Mox1 oxidase 9034-40-6,
Gonadotropin-releasing hormone 9081-34-9, 5.alpha. Reductase
50812-37-8, Glutathione S-transferase 60748-06-3, Gastrin 17
62010-37-1, GD3 65988-71-8, GD2 66456-69-7, GM4 66594-14-7, Quil A
80043-53-4, Gastrin-releasing peptide 83588-90-3, N-
Acetylglucosaminyltransferase V 83869-56-1, GM-CSF 89800-66-8,
Heparanase 120178-12-3, Telomerase 127464-60-2, Vascular endothelial
growth factor 140208-23-7, Plasminogen activator inhibitor-1
141256-04-4, QS21
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(weak antigens inserted with foreign T cell epitope as **vaccines**
)
IT 61512-21-8, Thymosin
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(.beta. 15; weak antigens inserted with foreign T cell epitope as
vaccines)
IT 9005-80-5, Inulin
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(.gamma.-; weak antigens inserted with foreign T cell epitope as
vaccines)

L37 ANSWER 5 OF 25 HCAPLUS COPYRIGHT 2001 ACS
AN 2000:144722 HCAPLUS
DN 132:185454
TI Use of anti-angiogenic agents for inhibiting vessel wall injury
IN Brown, Charles L., III; Gorlin, Steve
PA Global Vascular Concepts, Inc., USA
SO PCT Int. Appl., 29 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2000010552	A2	20000302	WO 1999-US19218	19990824
	WO 2000010552	A3	20001123		
	W:	AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
	RW:	GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			

AU 9956871 A1 20000314 AU 1999-56871 19990824
PRAI US 1998-97579 19980824
WO 1999-US19218 19990824
AB Use of anti-angiogenic agents to inhibit an undesirable response to
vessel
wall injury, including stent neointima, dialysis graft neointima,
vascular
graft-induced neointima, and the treatment of benign hypertrophic scar
formation as well as the treatment and passivation of unstable
atherosclerotic plaques are provided. The invention provides for the use
of catheter-based devices for enhancing the local delivery of
anti-angiogenic agents into the endothelial tissues of blood vessels of
the living body.
IC ICM A61K031-00
CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 1
IT Interleukin 1
Interleukin 12
Leukemia inhibitory factor
Protamines
Retinoids
Thrombospondins
Tumor necrosis factors
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(anti-angiogenic agents for inhibiting vessel wall injury)
IT 50-28-2, Estradiol, biological studies 50-35-1, Thalidomide 50-81-7D,
Ascorbic acid, ethers 52-01-7, Spironolactone 53-05-4,
Tetrahydrocortisone 53-86-1, Indomethacin 60-33-3, Linoleic acid,
biological studies 60-54-8, Tetracycline 68-96-2, 17.alpha.-
Hydroxyprogesterone 128-13-2, Ursodeoxycholic acid 145-63-1, Suramin
152-58-9, Cortexolone 302-79-4, Retinoic acid 362-07-2,
2-Methoxyestradiol 446-72-0, Genistein 465-21-4, Bufalin 566-35-8
2609-46-3, Amiloride 4431-00-9, Aurine tricarboxylic acid 10118-90-8,
Minocycline 12772-57-5, Radicicol 19545-26-7, Wortmannin
33069-62-4,
Taxol 34031-32-8, Auranofin 37270-94-3, Platelet factor 4
38096-31-0, Diaminoanthraquinone 38194-50-2, Sulindac 50903-99-6,
L-Name 53902-12-8, Tranilast 57381-26-7, Irsogladine
62571-86-2, Captopril 62996-74-1, Staurosporine 65646-68-6,
Fenretinide 70563-58-5, Herbimycin A 79831-76-8, Castanospermine
86090-08-6, Angiostatin 100827-28-9, Erbstatin 103909-75-7,
22-Oxa-1.alpha.-25-dihydroxyvitamin D3 105219-56-5, WEB 2086
110124-55-5, MDL 27032 125697-92-9, Lavendustin A 126509-46-4,
Eponemycin 129298-91-5, TNP-470 130370-60-4, BB-94 134633-29-7,
Tecogalan sodium 142186-14-9, FR-118487 148717-90-2, Squalamine
154039-60-8, Marimastat 171784-03-5, Louisianine A 171784-04-6,
Louisianine B 171784-06-8, Louisianine D 187888-07-9, Endostatin
188417-67-6, CM 101 204005-46-9, SU5416
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(anti-angiogenic agents for inhibiting vessel wall injury)
L37 ANSWER 6 OF 25 HCAPLUS COPYRIGHT 2001 ACS
AN 2000:15159 HCAPLUS
DN 132:73642
TI Acyl pseudodipeptides, preparation method, pharmaceutical compositions
containing them for therapeutic use
IN Bauer, Jacques; Martin, Olivier Richard

PA Om Pharma, Switz.
 SO PCT Int. Appl., 123 pp.
 CODEN: PIXXD2

DT Patent
 LA French

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2000000462	A1	20000106	WO 1999-IB1170	19990623
	W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	AU 9942848	A1	20000117	AU 1999-42848	19990623
PRAI	WO 1998-FR1396		19980630		
	WO 1999-IB1170		19990623		
OS	MARPAT 132:73642				
AB	The invention discloses N-acyl pseudodipeptides $\text{XA}(\text{CH}_2)_m\text{CH}(\text{NHR}_1)(\text{CH}_2)_n\text{CONH}(\text{CH}_2)_p\text{CH}(\text{NHR}_2)(\text{CH}_2)_q\text{BY}$ [R1, R2 = (un)satd. (un)branched (un)substituted C2-24 carboxylic acid; m, p, q = 1-10; n = 0-10; X, Y = H, phosphono, hydroxysulfonyl, dimethoxyphosphoryl, (C1-5 alkyl) carboxy, etc.; A, B = O, S, NH] and salts thereof. The invention also discloses pharmaceutical compns. contg. as active principle at least one of the above compds. The compds. have interesting pharmacol. properties which make them useful as medicines esp. as immunomodulators. The compds. are of interest in the treatment of immune deficiency diseases and diseases involving hyperimmune response, in the treatment of cancer, and as vaccine adjuvants. Their amphiphilic character makes them useful in drug delivery systems.				
IC	C07C237-00				
CC	1-7 (Pharmacology)				
	Section cross-reference(s): 15, 34, 63				
IT	Antitumor agents Dendritic cell Drug delivery systems Immunomodulators Lymphocyte Macrophage Monocyte Protective groups Reducing agents Vaccines (acyl pseudodipeptide prepn. and pharmaceutical compns. for therapeutic use)				
IT	Immunostimulants (adjuvants; acyl pseudodipeptide prepn. and pharmaceutical compns. for therapeutic use)				
IT	Proteins, specific or class RL: BPR (Biological process); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative); PROC (Process)				

(p70, **IL-12**; acyl pseudodipeptide prepn. and pharmaceutical compns. for therapeutic use)

IT **Interleukin 12**
 RL: BPR (Biological process); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative); PROC (Process)
 (p70; acyl pseudodipeptide prepn. and pharmaceutical compns. for therapeutic use)

IT **10102-43-9, Nitric oxide**, biological studies
 RL: BPR (Biological process); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative); PROC (Process)
 (macrophage; acyl pseudodipeptide prepn. and pharmaceutical compns. for therapeutic use)

RE.CNT 7

RE

- (1) Dai Ichi Seiyaku Co Ltd; JP 61227586 A 1986 HCAPLUS
- (2) Gwynfor, D; WO 9514026 A 1995 HCAPLUS
- (3) Miyajima, K; Chem Pharm Bull 1997, V45(6), P1089 HCAPLUS
- (4) Miyajima, K; Chem Pharm Bull 1997, V45(2), P312 HCAPLUS
- (5) Suhara, Y; Chem Pharm Bull 1994, V42(12), P2526 HCAPLUS

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L37 ANSWER 7 OF 25 HCAPLUS COPYRIGHT 2001 ACS

AN ~~2000:466559~~ HCAPLUS

DN 133:191684

TI **Interleukin-12 (IL-12) enhancement**
 of the cellular immune response against human immunodeficiency virus type 1 env antigen in a DNA prime/vaccinia virus boost **vaccine**
 regimen is time and dose dependent: suppressive effects of IL-12 boost are mediated by **nitric oxide**

AU Gherardi, M. Magdalena; Ramirez, Juan C.; Esteban, Mariano
 CS Department of Molecular and Cellular Biology, Centro Nacional de Biotecnologia, CSIC, Universidad Autonoma, Madrid, E-28049, Spain
 SO J. Virol. (2000), 74(14), 6278-6286
 CODEN: JOVIAM; ISSN: 0022-538X

PB American Society for Microbiology

DT Journal

LA English

AB The authors previously demonstrated that codelivery of interleukin-12 (IL-12) with the human immunodeficiency virus type 1 (HIV-1) Env antigen from a recombinant vaccinia virus (rVV) can enhance the specific anti-Env cell-mediated immune (CMI) response. Here, they investigated the effects of IL-12 in mice when it is expressed in a DNA prime/VV boost vaccine regimen. The delivery of IL-12 and Env product during priming with a DNA vector, followed by a booster with VV expressing the Env gene (rVVenv), was found to trigger the optimal CMI response compared with other immunization schedules studied. Significantly, if IL-12 is also delivered

as a booster from the viral vector, an impairment of the effects of IL-12 was obsd. involving nitric oxide (NO), since it was overcome by specific inhibitors of inducible NO synthase. NO caused transient immunosuppression rather than impairment of viral replication. Moreover, at certain viral doses, coadministration of the NO inhibitor during the booster resulted in IL-12-mediated enhancement of the specific CD8+ T-cell

response. In addn., the dose of the IL-12-encoding plasmid (pIL-12) and the route of administration of both vectors were relevant factors for

Date should be 9/13/98

Date is not given

optimal CMI responses. Maximal nos. of Env-specific CD8+ .gamma. interferon-secreting cells were obtained when 50 .mu.g of pIL-12 was administered i.m. at priming, followed by an i.v. rVVenv boost. The authors' results demonstrate, in a murine model, crit. parameters affecting the success of vaccination schedules based on a combination of DNA and VV vectors in conjunction with immunomodulators.

CC 15-2 (Immunochemistry)

ST **interleukin 12 immunomodulation HIV env DNA vaccine nitric oxide**

IT **Vaccines**
 (AIDS; **interleukin-12** enhancement of cellular immune response against HIV-1 env antigen in DNA prime/vaccinia virus boost **vaccine** regimen is time- and dose-dependent)

IT **Immunostimulants**
 (adjuvants; **interleukin-12** enhancement of cellular immune response against HIV-1 env antigen in DNA prime/vaccinia virus boost **vaccine** regimen is time- and dose-dependent)

IT **Immunity**
 (cell-mediated; **interleukin-12** enhancement of cellular immune response against HIV-1 env antigen in DNA prime/vaccinia virus boost **vaccine** regimen is time- and dose-dependent)

IT Human immunodeficiency virus 1
 Vaccinia virus
 Virus vectors
 (**interleukin-12** enhancement of cellular immune response against HIV-1 env antigen in DNA prime/vaccinia virus boost **vaccine** regimen is time- and dose-dependent)

IT Envelope proteins
Interleukin 12
 RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (**interleukin-12** enhancement of cellular immune response against HIV-1 env antigen in DNA prime/vaccinia virus boost **vaccine** regimen is time- and dose-dependent)

IT DNA
 RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (**vaccine; interleukin-12** enhancement of cellular immune response against HIV-1 env antigen in DNA prime/vaccinia virus boost **vaccine** regimen is time- and dose-dependent)

IT Anti-AIDS agents
 (**vaccines; interleukin-12** enhancement of cellular immune response against HIV-1 env antigen in DNA prime/vaccinia virus boost **vaccine** regimen is time- and dose-dependent)

IT 10102-43-9, **Nitric oxide**, biological studies
 RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
 (**interleukin-12** enhancement of cellular immune response against HIV-1 env antigen in DNA prime/vaccinia virus boost **vaccine** regimen is time and dose dependent and **nitric oxide** mediates suppressive effects of IL-12 boost)

RE.CNT 59

RE

- (1) Ahlers, J; J Immunol 1997, V158, P3947 HCAPLUS
- (2) Andre, S; J Virol 1998, V72, P1497 HCAPLUS
- (5) Boyer, J; Nat Med 1997, V3, P526 HCAPLUS
- (7) Caver, T; Vaccine 1999, V17, P1567 HCAPLUS
- (8) Chow, Y; J Virol 1997, V71, P169 HCAPLUS

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L37 ANSWER 8 OF 25 HCAPLUS COPYRIGHT 2001 ACS

AN 2000:262313 HCAPLUS

DN 133:72604

TI Direct Immunization of Malaria DNA **Vaccine** into the Liver by
Gene Gun Protects against Lethal Challenge of Plasmodium berghei
Sporozoite

AU Yoshida, Shigeto; Kashiwamura, Shin-Ichiro; Hosoya, Yoshinori; Luo,
Enjie;

CS Matsuoka, Hiroyuki; Ishii, Akira; Fujimura, Akio; Kobayashi, Eiji
Department of Medical Zoology, Jichi Medical School, Minamikawachimachi,
Tochigi, 329-0498, Japan

SO Biochem. Biophys. Res. Commun. (2000), 271(1), 107-115
CODEN: BBRCA9; ISSN: 0006-291X

PB Academic Press

DT Journal

LA English

AB The liver is the first target organ for malaria parasites immediately
after the bite of an infected mosquito. We studied local immunization of
malaria DNA vaccines at the site of the liver using a gene gun as a
useful

tool for in vivo transfection of foreign genes. A malaria DNA vaccine
consisting of the Plasmodium berghei circumsporozoite protein (PbCSP)

gene
plus the mouse IL-12 gene was bombarded directly by a gene gun into mouse
liver once or into the skin twice. A marked protective effect was

induced
by gene bombardment into the liver (more than 71%) compared with that
into

the skin (less than 33%). A Th1-type immune response and high prodn. of
iNOS were obsd. in the hepatic lymphocytes from mice bombarded into the
liver, resulting in more effective protection compared with those
bombarded into the skin. These results provide an important implication
on the development of efficient malaria vaccine strategies. (c) 2000
Academic Press.

CC 15-2 (Immunochimistry)

Section cross-reference(s): 14

ST gene gun malaria **vaccine** Plasmodium IL12

IT **Vaccines**

(antimalarial; gene gun mediated malaria DNA vaccination into liver
and
protection against lethal challenge of Plasmodium berghei)

IT DNA

Interleukin 12

RL: BAC (Biological activity or effector, except adverse); THU
(Therapeutic use); BIOL (Biological study); USES (Uses)

(gene gun mediated malaria DNA vaccination into liver and protection
against lethal challenge of Plasmodium berghei)

IT Antimalarials

(**vaccines**; gene gun mediated malaria DNA vaccination into
liver and protection against, lethal challenge of Plasmodium berghei)

IT 125978-95-2, Nitric oxide Synthase
 RL: BOC (Biological occurrence); BIOL (Biological study); OCCU
 (Occurrence)
 (inducible; gene gun mediated malaria DNA vaccination into liver and
 protection against lethal challenge of Plasmodium berghei)

RE.CNT 37

RE

- (1) Akbari, O; J Exp Med 1999, V189, P169 HCAPLUS
- (3) Bharadwaj, A; Infect Immun 1998, V66, P3232 HCAPLUS
- (4) Blankenstein, T; Eur J Immunol 1990, V20, P935 HCAPLUS
- (6) Doolan, D; J Exp Med 1996, V183, P1739 HCAPLUS
- (7) Doolan, D; J Immunol 1999, V163, P884 HCAPLUS

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L37 ANSWER 9 OF 25 USPATFULL

AN 1999:84987 USPATFULL

TI Use of IL-12 and IFN.alpha. for the treatment of
 infectious diseases

IN Alber, Gottfried, Leipzig, Germany, Federal Republic of
 Carr, Jacqueline Anne, Ware, United Kingdom
 Mattner, Frank Albert, Mailand, Italy
 Mulqueen, Michael John, Rochford, United Kingdom
 Palmer, Kathrin, Munchenstein, Switzerland
 Rogerson, Jane Andre Louise, St. Albans, United Kingdom

PA Hoffmann-La Roche Inc., Nutley, NJ, United States (U.S. corporation)

PI US 5928636 19990727

AI US 1997-845973 19970430 (8)

PRAI GB 1996-9932 19960513

DT Utility

EXNAM Primary Examiner: Mertz, Prema

LREP Johnson, George W.; Epstein, William H.; Buchholz, Briana C.

CLMN Number of Claims: 42

ECL Exemplary Claim: 1

DRWN No Drawings

LN.CNT 629

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention provides a combination of IL-12
 and IFN.alpha. together with a pharmaceutically acceptable carrier
 useful for treatment and prophylaxis of infectious diseases, preferably
 chronic infectious diseases and more preferably viral infections, e.g.
 HSV, HIV, Hepatitis B, Hepatitis C, papilloma etc., bacterial
 infections, e.g. tuberculosis, salmonellosis, listeriosis, etc., and
 parasite infections, e.g. malaria, leishmaniasis, and schistosomiasis.
 These compositions are characterized by the synergistic interaction of
 IL-12 and IFN.alpha.. The present invention also
 provides the use of the above combination for the treatment and
 prophylaxis of infectious diseases.

L37 ANSWER 10 OF 25 USPATFULL

AN 1999:81550 USPATFULL

TI Recombinant fowlpox viruses and uses thereof

IN Cochran, Mark D., Carlsbad, CA, United States

Junker, David E., San Diego, CA, United States

PA Syntro Corporation, Lenexa, KS, United States (U.S. corporation)

PI US 5925358 19990720

AI US 1995-484575 19950607 (8)

RLI Continuation-in-part of Ser. No. WO 1994-US2252, filed on 28 Feb 1994

which is a continuation of Ser. No. US 1993-24156, filed on 26 Feb 1993,

now abandoned

DT Utility

EXNAM Primary Examiner: Mosher, Mary E.

LREP White, John P. Cooper & Dunham LLP

CLMN Number of Claims: 24

ECL Exemplary Claim: 1

DRWN 11 Drawing Figure(s); 11 Drawing Page(s)

LN.CNT 3589

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB This invention provides a recombinant fowlpox virus comprising a foreign

DNA sequence inserted into the fowlpox virus genomic DNA, wherein the foreign DNA sequence is inserted within a 2.8 kB EcoRI fragment of the fowlpox virus genomic DNA and is capable of being expressed in a fowlpox

virus infected host cell. The invention further provides homology vectors, vaccines and methods of immunization.

L37 ANSWER 11 OF 25 USPATFULL

AN 1999:78766 USPATFULL

TI Methods for in vivo reduction of iron levels and compositions useful therefor

IN Lai, Ching-San, Encinitas, CA, United States

PA Medinox, Inc., San Diego, CA, United States (U.S. corporation)

PI US 5922761 19990713

AI US 1996-708552 19960906 (8)

DT Utility

EXNAM Primary Examiner: Criares, Theodore J.

LREP Gray Cary Ware & Freidenrich LLP; Reiter, Stephen E.

CLMN Number of Claims: 40

ECL Exemplary Claim: 1

DRWN 4 Drawing Figure(s); 3 Drawing Page(s)

LN.CNT 1065

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB In accordance with the present invention, there are provided methods for

the in vivo reduction of free iron ion levels in a mammalian subject. The present invention employs a scavenging approach whereby free iron ions are bound in vivo to a suitable physiologically compatible scavenger. The resulting complex renders the free iron ions harmless, and is eventually excreted in the urine of the host. Further in accordance with the present invention, there are provided compositions and formulations useful for carrying out the above-described methods.

An

exemplary scavenger contemplated for use in the practice of the present invention is a dithiocarbamate-containing composition. This material binds to free iron ions, forming a stable, water-soluble dithiocarbamate-iron complex. The present invention relates to methods for reducing in vivo levels of free iron ions as a means of treating subjects afflicted with iron overload and non-iron overload diseases and/or conditions, such as thalassemia, anemia hereditary hemochromatosis, hemodialysis, stroke and rheumatoid arthritis. Dithiocarbamate-containing scavengers are administered to a host in

need

of such treatment; these scavengers interact with in vivo forming a

the stable dithiocarbamate-metal complex, which is then filtered through the kidneys, concentrated in the urine, and eventually excreted by the subject, thereby reducing in vivo levels of free iron ions.

L37 ANSWER 12 OF 25 HCAPLUS COPYRIGHT 2001 ACS
 AN 1999:194016 HCAPLUS
 DN 130:236450
 TI Mucosal cytotoxic T lymphocyte responses
 IN Berzofsky, Jay A.; Belyakov, Igor M.; Derby, Michael A.; Kelsall, Brian L.; Strober, Warren
 PA United States Dept. of Health and Human Services, USA
 SO PCT Int. Appl., 86 pp.
 CODEN: PIXXD2
 DT Patent
 LA English
 FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9912563	A2	19990318	WO 1998-US19028	19980911
	WO 9912563	A3	19990527		
	W:	AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
	RW:	GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			
	AU 9893862	A1	19990329	AU 1998-93862	19980911
	EP 1011720	A2	20000628	EP 1998-946965	19980911
	R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI			
PRAI	US 1997-58523		19970911		
	US 1998-74894		19980217		
	WO 1998-US19028		19980911		
AB	The invention provides methods for induction of an antigen-specific, mucosal cytotoxic T lymphocyte response useful in preventing and treating infections with pathogens that gain entry via a mucosal surface. Sol. antigens derived from pathogenic virus or bacteria or protozoan, such as HIV-1, influenza virus, rotavirus, or others are used in cluster peptide vaccine constructs.				
IC	ICM A61K039-00 ICS A61K039-39; A61K038-19; A61K039-21; A61K039-145; A61K039-02; A61K039-002; A61K009-00; C07K014-16; A61K039-39; A61K038-19				
CC	15-2 (Immunochemistry) Section cross-reference(s): 63				
ST	mucosal cytotoxic T lymphocyte antigen vaccine				
IT	Vaccines (cluster peptide vaccine construct; sol. antigen for induction of mucosal cytotoxic T lymphocyte responses)				
IT	Adjuvants (immunological) Animal virus Bacteria (Eubacteria) CD8-positive T cell Cat (Felis catus) Cytotoxic T cell				

Drug carriers (drug delivery systems)
 Giardia lamblia
 Hepatitis A virus
 Human immunodeficiency virus
 Human immunodeficiency virus 1
 Infection
 Influenza virus
 Listeria monocytogenes
 Mammal (Mammalia)
 Melanoma
 Micelles
 Mouse
 Pathogen
 Primate
 Protein sequences
 Protozoa
 Rotavirus
 Surfactants
 Viral infection
 (sol. antigen for induction of mucosal cytotoxic T lymphocyte responses)
 IT Antibodies
 Caprylic/capric triglycerides
 Cholera toxin
 Cytokines
 Enamines
 Heat labile enterotoxin
 Interferon .gamma.
 Interleukin 12
 Interleukin 2
 Interleukin 7
 Medium-chain fatty acids
 Pertussis toxin
 Polyoxyalkylenes, biological studies
 Prostate-specific antigen
 Protein A
 Tumor necrosis factor .alpha.
 Tumor-associated antigen
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (sol. antigen for induction of mucosal cytotoxic T lymphocyte responses)
 IT **10102-43-9, Nitric oxide**, biological studies
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (donor; sol. antigen for induction of mucosal cytotoxic T lymphocyte responses)
 L37 ANSWER 13 OF 25 HCAPLUS COPYRIGHT 2001 ACS
 AN 1999:275426 HCAPLUS
 DN 131:72419
 TI Immune-stimulating complexes induce an IL-12-dependent cascade of innate immune responses
 AU Smith, Rosemary E.; Donachie, Anne M.; Grdic, Dubravka; Lycke, Nils; Mowat, Allan McI.
 CS Department of Immunology, University of Glasgow, Western Infirmary, Glasgow, G11 6NT, UK
 SO J. Immunol. (1999), 162(9), 5536-5546
 CODEN: JOIMA3; ISSN: 0022-1767

data not good

PB American Association of Immunologists

DT Journal

LA English

AB The development of subunit vaccines requires the use of adjuvants that act

by stimulating components of the innate immune response.

Immune-stimulating complexes (ISCOMS) contg. the saponin adjuvant Quil A are potential vaccine vectors that induce a wide range of Ag-specific responses in vivo encompassing both humoral and CD4 and CD8 cell-mediated immune responses. ISCOMS are active by both parenteral and mucosal routes, but the basis for their adjuvant properties is unknown. Here we have investigated the ability of ISCOMS to recruit and activate innate immune responses as measured in peritoneal exudate cells. The i.p. injection of ISCOMS induced intense local inflammation, with early recruitment of neutrophils and mast cells followed by macrophages, dendritic cells, and lymphocytes. Many of the recruited cells had phenotypic evidence of activation and secreted a no. of inflammatory mediators, including nitric oxide, reactive oxygen intermediates, IL-1, IL-6, IL-12, and IFN- γ . Of the factors that we investigated

further

only IL-12 appeared to be essential for the immunogenicity of ISCOMS, as IL-6-and inducible nitric oxide synthase knockout (KO) mice developed normal immune responses to OVA in ISCOMS, whereas these responses were markedly reduced in IL-12KO mice. The recruitment of peritoneal exudate cells following an injection of ISCOMS was impaired in IL-12KO mice, indicating a role for IL-12 in establishing the proinflammatory cascade. Thus, ISCOMS prime Ag-specific immune responses at least in part by activating IL-12-dependent aspects of the innate immune system.

CC 15-2 (Immunochemistry)

ST ISCOM **interleukin 12** innate immune response

IT **Immunostimulants**

(adjuvants, ISCOMs; **interleukin-12**

-dependent immune responses induced by ISCOMS)

IT Dendritic cell

Immunostimulation

Lymphocyte

Macrophage

Mast cell

Neutrophil

(effect of ISCOMS on immune cells in relation to **interleukin-12**-dependent immune responses)

IT Interleukin 1

Interleukin 6

Reactive oxygen species

RL: MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)

(effect of ISCOMS on immune cells in relation to **interleukin-12**-dependent immune responses)

IT Inflammation

(effect of ISCOMS on immune cells in relation to **interleukin-12**-dependent immune responses and inflammation)

IT **Interleukin 12**

RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**interleukin-12**-dependent immune responses induced by ISCOMS)

IT Interferons

RL: MFM (Metabolic formation); BIOL (Biological study); FORM (Formation,

nonpreparative)
 (.gamma.; effect of ISCOMS on immune cells in relation to
interleukin-12-dependent immune responses)
 IT 7782-44-7D, Oxygen, reactive species 10102-43-9, **Nitric
 oxide**, biological studies
 RL: MFM (Metabolic formation); BIOL (Biological study); FORM (Formation,
 nonpreparative)
 (effect of ISCOMS on immune cells in relation to **interleukin-
 12**-dependent immune responses)
 IT 66594-14-7, Quil A
 RL: BAC (Biological activity or effector, except adverse); BIOL
 (Biological study)
 (**interleukin-12**-dependent immune responses induced
 by ISCOMS contg. Quil A)
 RE.CNT 46
 RE
 (1) Abdi, K; J Immunol 1997, V159, P3148 HCAPLUS
 (2) Albert, M; Nature 1998, V392, P86 HCAPLUS
 (3) Baumann, H; Immunol Today 1994, V15, P74 HCAPLUS
 (4) Behboudi, S; Clin Exp Immunol 1996, V105, P26 HCAPLUS
 (5) Behboudi, S; Cytokine 1997, V9, P682 HCAPLUS
 ALL CITATIONS AVAILABLE IN THE RE FORMAT

 L37 ANSWER 14 OF 25 HCAPLUS COPYRIGHT 2001 ACS
 AN 1999:524711 HCAPLUS
 DN 131:270562
 TI Immune effector mechanisms in malaria
 AU Good, Michael F.; Doolan, Denise L.
 CS The Cooperative Research Centre for Vaccine Technology, The Queensland
 Institute of Medical Research, Queensland, 4029, Australia
 SO Curr. Opin. Immunol. (1999), 11(4), 412-419
 CODEN: COPIEL; ISSN: 0952-7915
 PB Current Biology Publications
 DT Journal; General Review
 LA English
 AB A review with 74 refs. Malaria, a disease responsible for immense human
 suffering, is caused by infection with Plasmodium spp. parasites, which
 have a very complex life cycle - antigenically unique stages infect
 different tissues of the body. This review details recent developments
 in
 our understanding of immunity both to pre-erythrocytic stage antigens and
 to erythrocytic stage antigens. The former is largely mediated via CD8+
 T
 cells and involves IFN-.gamma., nitric oxide, IL-12 and natural killer
 cells; the latter varies (in different hosts and with different
 parasites)
 but is largely mediated by antibody, helper T cells, nitric oxide and
 .gamma..delta. T cells. The recent progress towards clin. trials of
 vaccine candidates against both the pre-erythrocytic stage and
 erythrocytic stage is also summarized, in particular the use of
 heterologous prime/boost strategies for the former and the use of MSP1 as
 a candidate vaccine for the latter.
 CC 15-0 (Immunochemistry)
 Section cross-reference(s): 14
 ST review malaria **vaccine** T lymphocyte cytokine
 IT **Vaccines**
 (antimalarial; immune effector mechanisms in malaria)

IT Antibodies

Interleukin 12

RL: BAC (Biological activity or effector, except adverse); BOC
(Biological
occurrence); BIOL (Biological study); OCCU (Occurrence)
(immune effector mechanisms in malaria)

IT Antimalarials

(vaccines; immune effector mechanisms in malaria)

IT 10102-43-9, Nitric oxide, biological studies

RL: BAC (Biological activity or effector, except adverse); BOC
(Biological
occurrence); BIOL (Biological study); OCCU (Occurrence)
(immune effector mechanisms in malaria)

RE.CNT 74

RE

- (1) Amante, F; J Immunol 1997, V159, P5535 HCAPLUS
 - (2) Amante, F; Parasite Immunol 1997, V19, P111 HCAPLUS
 - (4) Anders, R; Vaccine 1998, V16, P240 HCAPLUS
 - (5) Berzins, K; Malaria Vaccine Development: A Multi-Immune Response Approach 1996, P105 HCAPLUS
 - (8) Bull, P; Nat Med 1998, V4, P358 HCAPLUS
- ALL CITATIONS AVAILABLE IN THE RE FORMAT

L37 ANSWER 15 OF 25 HCAPLUS COPYRIGHT 2001 ACS

AN 1999:45527 HCAPLUS

DN 130:316478

TI Oral vaccination with immune stimulating complexes

AU McI Mowat, Allan; Smith, Rosemary E.; Donachie, Anne M.; Furrie, Elizabeth; Grdic, Dubravka; Lycke, Nils

CS Western Infirmary, Department of Immunology, University of Glasgow, Glasgow, G11 6NT, UK

SO Immunol. Lett. (1999), 65(1,2), 133-140 ✓

CODEN: IMLED6; ISSN: 0165-2478

PB Elsevier Science Ireland Ltd.

DT Journal

LA English

AB There is a need for non-living adjuvant vectors which will induce a full range of local and systemic immune responses to orally administered purified antigens. Here the authors describe the authors' experience

with

lipophilic immune stimulating complexes (ISCOMS) contg. the saponin adjuvant Quil A. When given orally, ISCOMS contg. the model protein antigen ovalbumin (OVA) induce a wide range of systemic immune responses, including Th1 and Th2 CD4 dependent activity, class I MHC restricted cytotoxic T-cell responses and local prodn. of secretory IgA antibodies. More recent results indicate that ISCOMS may act partly by enhancing the uptake of protein from the gut. In addn., i.p. injection of ISCOMS recruits and activates many components of the innate immune system, including neutrophils, macrophages, and dendritic cells. In parallel, there is increased prodn. of nitric oxide (NO), reactive oxygen intermediates (ROI), interleukins (IL) 1, 6, 12, and .gamma. interferon (.gamma.IFN). Of these factors, only IL-12 is essential for the immunogenicity of ISCOMS in vivo, as mucosal and systemic responses to ISCOMS are reduced in IL-12KO mice, but not in IL-4KO, IL-6KO, inducible NO synthase (iNOS) KO, or .gamma.IFN receptor KO mice. The authors propose that ISCOMS act by targeting antigen and adjuvant to macrophages and/or dendritic cells. This pathway may be amenable to exploitation for

vaccine development, esp. if combined with another vector with a different mucosal adjuvant profile, such as cholera toxin.

CC 63-3 (Pharmaceuticals)
Section cross-reference(s): 15

ST oral **vaccine** mucosal immunity ISCOM

IT **Interleukin 12**
RL: BAC (Biological activity or effector, except adverse); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)
(formation by inflammatory cell in recruitment by mucosal immunogenicity of ISCOMS)

IT Oral **vaccines**
(mucosal immunogenicity of ISCOMS is assocd. with increased antigen uptake by intestine and inflammatory cell recruitment in relation to)

IT **10102-43-9, Nitric oxide**, biological studies
RL: MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)
(formation by inflammatory cell in recruitment by mucosal immunogenicity of ISCOMS)

RE.CNT 33

RE
(1) Banchereau, J; Nature 1998, V392, P245 HCAPLUS
(3) Claassen, I; Adv Exp Med Biol 1995, V371B, P1485 HCAPLUS
(4) Claassen, I; Eur J Immunol 1995, V25, P1446 HCAPLUS
(5) Cox, J; Vaccine Design: the Role of Cytokine Networks 1997, V293, P33 HCAPLUS
(7) Erturk, M; J Gen Virol 1989, V70, P2149 HCAPLUS

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L37 ANSWER 16 OF 25 HCAPLUS COPYRIGHT 2001 ACS

AN 1999:294972 HCAPLUS

DN 131:143293

TI Mechanism and control of recombinant murine **interleukin-12**-induced immunosuppression

AU Koblish, Holly Kurzawa

CS Univ. of Pennsylvania, Philadelphia, PA, USA

SO (1998) 123 pp. Avail.: UMI, Order No. DA9913484
From: Diss. Abstr. Int., B 1999, 59(11), 5772

DT Dissertation

LA English

AB Unavailable

CC 15-5 (Immunochemistry)

ST **interleukin 12** antitumor immunosuppression cancer
vaccine; nitric oxide inhibitor tumor
vaccine adjuvant

IT **Vaccines**
(cancer; mechanism and control of recombinant murine **interleukin-12**-induced immunosuppression)

IT Antitumor agents
(effect; mechanism and control of recombinant murine **interleukin-12**-induced immunosuppression)

IT Immunosuppression
(mechanism and control of recombinant murine **interleukin-12**-induced immunosuppression)

IT **Interleukin 12**
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BIOL (Biological study)

(mechanism and control of recombinant murine **interleukin-12**-induced immunosuppression)

IT Neoplasm
(**vaccine**; mechanism and control of recombinant murine **interleukin-12**-induced immunosuppression)

IT 10102-43-9, **Nitric oxide**, biological studies
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(inhibitor; mechanism and control of recombinant murine **interleukin-12**-induced immunosuppression)

L37 ANSWER 17 OF 25 USPATFULL ✓

AN 1998:154309 USPATFULL

TI Method for in vivo reduction of **nitric oxide** levels and compositions useful therefor

IN Lai, Ching-San, Encinitas, CA, United States

PA MCW Research Foundation, Milwaukee, WI, United States (U.S. corporation)

PI US 5847004 19981208

AI US 1996-767125 19961209 (8)

RLI Continuation-in-part of Ser. No. US 1995-554196, filed on 6 Nov 1995 which is a continuation-in-part of Ser. No. US 1995-459518, filed on 2 Jun 1995, now patented, Pat. No. US 5741815

DT Utility

EXNAM Primary Examiner: Rotman, Alan L.; Assistant Examiner: Smith, Lyman H.

LREP Gray Cary Ware and Freidenrich; Reiter, Stephen E.

CLMN Number of Claims: 33

ECL Exemplary Claim: 1

DRWN 13 Drawing Figure(s); 6 Drawing Page(s)

LN.CNT 1485

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB In accordance with the present invention, there are provided methods for

the in vivo reduction of **nitric oxide** levels in a mammalian subject. In contrast to the inhibitory approach described in the prior art (i.e., wherein the function of the enzymes responsible for **nitric oxide** production is inhibited), the present invention employs a scavenging approach whereby overproduced **nitric oxide** is bound in vivo to a suitable **nitric oxide** scavenger. The resulting complex renders the **nitric oxide** harmless, and is eventually excreted in the urine of the host. An exemplary **nitric oxide** scavenger contemplated for use in the practice of the present invention is a dithiocarbamate-ferrous iron complex. This complex binds to .NO, forming a stable, water-soluble NO-containing complex having a characteristic three-line spectrum (indicative of a mononitrosyl-Fe complex) which can readily be detected at ambient temperatures by electron paramagnetic resonance (EPR) spectroscopy. The present invention relates to methods for reducing in vivo levels of .NO as a means of treating subjects afflicted with inflammatory and/or infectious disease. **Nitric oxide** scavengers are administered to a host in need of such treatment; these scavengers interact with in vivo produced .NO, forming a stable NO-containing complex. The NO-containing complex is then filtered through the kidneys, concentrated in the urine, and eventually excreted by the subject,

thereby reducing in vivo .NO levels.

L37 ANSWER 18 OF 25 USPATFULL
 AN 1998:57964 USPATFULL
 TI Methods for in vivo reduction of **nitric oxide** levels
 and compositions useful therefor
 IN Lai, Ching-San, Brookfield, WI, United States
 PA MCW Research Foundation, Inc., Milwaukee, WI, United States (U.S.
 corporation)
 PI US 5756540 19980526
 AI US 1995-459518 19950602 (8)
 DT Utility
 EXNAM Primary Examiner: Nazario-Gonzalez, Porfirio
 LREP Pretty, Schroeder, Brueggemann & Clark; Reiter, Stephen E.
 CLMN Number of Claims: 39
 ECL Exemplary Claim: 1,2,14
 DRWN 13 Drawing Figure(s); 6 Drawing Page(s)
 LN.CNT 1409
 CAS INDEXING IS AVAILABLE FOR THIS PATENT.
 AB In accordance with the present invention, there are provided methods
 for
 the in vivo reduction of **nitric oxide** levels in a
 mammalian subject. In contrast to the inhibitory approach described in
 the prior art (i.e., wherein the function of the enzymes responsible
 for
nitric oxide production is inhibited), the present
 invention employs a scavenging approach whereby overproduced
nitric oxide is bound in vivo to a suitable
nitric oxide scavenger. The resulting complex renders
 the **nitric oxide** harmless, and is eventually
 excreted in the urine of the host. Further in accordance with the
 present invention, there are provided compositions and formulations
 useful for carrying out the above-described methods. An exemplary
nitric oxide scavenger contemplated for use in the
 practice of the present invention is a dithiocarbamate-ferrous iron
 complex. The present invention relates to methods for reducing in vivo
 levels of .multidot.NO as a means of treating subjects afflicted with
 inflammatory and/or infectious disease. Dithiocarbamate-containing
nitric oxide scavengers are administered to a host in
 need of such treatment; these scavengers interact with in vivo produced
 .multidot.NO, forming a stable dithiocarbamate-metal-NO complex. The
 NO-containing complex is then filtered through the kidneys,
 concentrated
 in the urine, and eventually excreted by the subject, thereby reducing
 in vivo .multidot.NO levels.

L37 ANSWER 19 OF 25 USPATFULL
 AN 1998:42383 USPATFULL
 TI Methods for in vivo reduction of **nitric oxide** levels
 and compositions useful therefor
 IN Lai, Ching-San, 17765 Bolter La., Brookfield, WI, United States 53045
 PI US 5741815 19980421
 AI US 1995-554196 19951106 (8)
 RLI Continuation-in-part of Ser. No. US 1995-459518, filed on 2 Jun 1995
 DT Utility
 EXNAM Primary Examiner: Ivy, C. Warren; Assistant Examiner: Smith, Lyman H.
 LREP Gray Cary Ware & Freidenrich; Reiter, Stephen E.

CLMN Number of Claims: 41
ECL Exemplary Claim: 1
DRWN 13 Drawing Figure(s); 6 Drawing Page(s)
LN.CNT 1537

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention employs a scavenging approach whereby overproduced

nitric oxide is bound in vivo to a suitable **nitric oxide** scavenger. The resulting complex renders the **nitric oxide** harmless, and is eventually excreted in the urine of the host. Further in accordance with the present invention, there are provided compositions and formulations useful for carrying out the above-described methods. An exemplary **nitric oxide** scavenger contemplated for use in the practice of the present invention is a dithiocarbamate-ferrous iron complex. This complex binds to .NO, forming a stable, water-soluble dithiocarbamate-iron-NO complex having a characteristic three-line spectrum (indicative of a mononitrosyl-Fe complex) which can readily be detected at ambient temperatures by electron paramagnetic resonance (EPR) spectroscopy. The present invention relates to methods for reducing in vivo levels of .NO as a means of treating subjects afflicted with inflammatory and/or infectious disease. Dithiocarbamate-containing **nitric oxide** scavengers are administered to a host in need of such treatment; these scavengers interact with in vivo produced .NO, forming a stable dithiocarbamate-metal-NO complex. The NO-containing complex is then filtered through the kidneys, concentrated in the urine, and eventually excreted by the subject, thereby reducing in vivo .NO levels.

L37 ANSWER 20 OF 25 HCAPLUS COPYRIGHT 2001 ACS

AN 1998:717539 HCAPLUS

DN 130:80197

TI Immune suppression by recombinant interleukin (rIL)-12 involves interferon

.gamma. induction of **nitric oxide** synthase 2 (iNOS) activity: inhibitors of NO generation reveal the extent of rIL-12 **vaccine adjuvant** effect

AU Koblisch, Holly Kurzawa; Hunter, Christopher A.; Wysocka, Maria; Trinchieri, Giorgio; Lee, William M. F.

CS Cell and Molecular Biology Graduate Group, Cancer Center, and Institute for Human Gene Therapy, School of Medicine, University of Pennsylvania, Philadelphia, PA, 19104, USA

SO J. Exp. Med. (1998), 188(9), 1603-1610
CODEN: JEMEAU; ISSN: 0022-1007

PB Rockefeller University Press

DT Journal

LA English

AB Recombinant interleukin 12 (IL-12) can profoundly suppress cellular immune responses in mice. To define the underlying mechanism, recombinant murine

(rm)IL-12 was given to C57BL/6 mice undergoing alloimmunization and found to transiently but profoundly suppress in vivo and in vitro allogeneic responses and in vitro splenocyte mitogenic responses. Use of neutralizing antibodies and genetically deficient mice showed that

IFN-.gamma. (but not TNF-.alpha.) mediated rmIL-12-induced immunosuppression. Splenocyte fractionation studies revealed that adherent cells from rmIL-12-treated mice suppressed the mitogenic response

of normal nonadherent cells to Con A and IL-2. Addn. of an inhibitor of nitric oxide synthase (NOS) restored mitogenic responses, and inducible (i)NOS-/- mice were not immunosuppressed by rmIL-12. These results support the view that suppression of T cell responses is due to NO produced by macrophages responding to the high levels of IFN-.gamma. induced by rmIL-12. When a NOS inhibitor was given with rmIL-12 during vaccination of A/J mice with irradiated SCK tumor cells,

immunosuppression

was averted and the extent of rmIL-12's ability to enhance induction of protective antitumor immunity was revealed. This demonstrates that rmIL-12 is an effective vaccine adjuvant whose efficacy may be masked by its transient immunosuppressive effect.

CC 15-5 (Immunochemistry)

ST immunosuppression **interleukin 12** interferon gamma
nitric oxide synthase; **vaccine**
adjuvant interleukin 12 immunosuppression

IT **Vaccines**

(antitumor; **interleukin-12 vaccine**
adjuvant effect as revealed by inhibition of **nitric**
oxide formation)

IT Immunosuppression

(immunosuppression by **interleukin-12** involves
interferon .gamma. induction of **nitric oxide**
synthase 2)

IT **Interleukin 12**

RL: BAC (Biological activity or effector, except adverse); BIOL
(Biological study)

(immunosuppression by **interleukin-12** involves
interferon .gamma. induction of **nitric oxide**
synthase 2)

IT Interferon .gamma.

RL: MFM (Metabolic formation); BIOL (Biological study); FORM (Formation,
nonpreparative)

(immunosuppression by **interleukin-12** involves
interferon .gamma. induction of **nitric oxide**
synthase 2)

IT **Adjuvants** (immunological)

(**interleukin-12 vaccine adjuvant**
effect as revealed by inhibition of **nitric oxide**
formation)

IT **125978-95-2, Nitric oxide** synthase

RL: BPR (Biological process); BIOL (Biological study); PROC (Process)

(2; immunosuppression by **interleukin-12** involves
interferon .gamma. induction of **nitric oxide**
synthase 2)

IT **10102-43-9, Nitric oxide**, biological studies

RL: MFM (Metabolic formation); BIOL (Biological study); FORM (Formation,
nonpreparative)

(immunosuppression by **interleukin-12** involves
interferon .gamma. induction of **nitric oxide**
synthase 2)

RE.CNT 31

RE

- (1) Atkins, M; Clin Cancer Res 1997, V3, P409 HCAPLUS
- (2) Bingisser, R; J Immunol 1998, V160, P5729 HCAPLUS
- (3) Brunda, M; Res Immunol 1995, V146, P622 HCAPLUS
- (4) Candolfi, E; Infect Immun 1994, V62, P1995 HCAPLUS
- (5) Candolfi, E; Infect Immun 1995, V63, P751 HCAPLUS

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L37 ANSWER 21 OF 25 HCAPLUS COPYRIGHT 2001 ACS
 AN 1998:503172 HCAPLUS
 DN 129:215611
 TI Control of IL-12 and IFN-.gamma. production in
 response to live or dead bacteria by TNF and other factors
 AU Zhan, Yifan; Cheers, Christina
 CS Department Microbiology, University Melbourne, Parkville, 3055, Australia
 SO J. Immunol. (1998), 161(3), 1447-1453
 CODEN: JOIMA3; ISSN: 0022-1767
 PB American Association of Immunologists
 DT Journal
 LA English
 AB When mice were infected i.v. with either Listeria monocytogenes or
 Brucella abortus, bioactive IL-12 was briefly detected in serum and
 supernatants of spleen homogenates immediately ex vivo. Although the
 time scale was more prolonged for the more slowly growing B. abortus, in both
 instances IL-12 prodn. ceased while bacteria still persisted in high nos.
 Prodn. of IL-12, detected in serum and spleen, was neither increased nor
 prolonged by injecting Abs to IL-10 or IL-4. In contrast with live
 organisms, heat-killed bacteria did not induce detectable IL-12 in vivo
 and were less efficient when added in vitro to resident peritoneal cells
 or spleen cells. Mice lacking the receptors for TNF (TNFR-/- mice) were
 severely deficient in IL-12 prodn., suggesting a controlling role for
 TNF, which the authors have previously shown to be triggered by live, rather
 than dead, bacteria. Infection in the TNFR-/- mice was exacerbated,
 although in the Brucella-infected mice splenomegaly, the main indicator
 of immunopathol., was reduced. Prodn. of NO by macrophages was deficient,
 but the TNFR-/- mice were not deficient in IFN-.gamma. prodn. In addn.
 to being poor inducers of IL-12, killed bacteria actively suppressed IL-12
 prodn. in response to live bacteria, by mechanism(s) unknown. The
 implications of these findings are discussed in light of the fact that
 only live bacteria satisfactorily induce cell-mediated immunity to
 infection.
 CC 15-8 (Immunochemistry)
 ST **interleukin 12** live dead bacteria TNF; interferon
 gamma live dead bacteria TNF; tumor necrosis factor cytokine bacterial
 infection
 IT Bacterial infection
 Brucella melitensis
 Listeria monocytogenes
 (interleukin-12 and interferon .gamma. formation
 control in response to live or dead bacteria by tumor necrosis factor)
 IT Tumor necrosis factors
 RL: BAC (Biological activity or effector, except adverse); BIOL
 (Biological study)
 (interleukin-12 and interferon .gamma. formation

control in response to live or dead bacteria by tumor necrosis factor)

IT Interferon .gamma.
 RL: MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)
 (interleukin-12 and interferon .gamma. formation
 control in response to live or dead bacteria by tumor necrosis factor)

IT Interleukin 12
 RL: MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)
 (interleukin-12 and interferon .gamma. formation
 control in response to live or dead bacteria by tumor necrosis factor)

IT Vaccines
 (interleukin-12 and interferon .gamma. formation
 control in response to live or dead bacteria by tumor necrosis factor in relation to)

IT 10102-43-9, Nitric oxide, biological studies
 RL: MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)
 (interleukin-12 and interferon .gamma. formation
 control in response to live or dead bacteria by tumor necrosis factor)

L37 ANSWER 22 OF 25 HCAPLUS COPYRIGHT 2001 ACS
 AN 1998:571676 HCAPLUS
 DN 129:314792
 TI Expression of cytokine genes in Aotus monkeys immunized with synthetic and recombinant Plasmodium vivax and P. falciparum antigens
 AU Duque, S.; Montenegro-James, S.; Arevalo-Herrera, M.; Praba, A. D.; Villinger, F.; Herrera, S.; James, M. A.
 CS Instituto Nacional de Salud, Bogota, Colombia
 SO Ann. Trop. Med. Parasitol. (1998), 92(5), 553-559
 CODEN: ATMPA2; ISSN: 0003-4983
 PB Carfax Publishing Ltd.
 DT Journal
 LA English
 AB Cytokine responses in human host-protective immunity to malaria have yet to be completely elucidated. No data appear to exist on the cytokine patterns in non-human primate models immunized with malarial antigens. Expression of mRNA transcripts of 10 cytokines, the adhesion mol. ICAM-1, and inducible nitric oxide synthase (iNOS) in peripheral-blood mononuclear cells (PBMC) from 9 Aotus monkeys was analyzed by reverse-transcriptase PCR. Five of the monkeys had been immunized with multiple-antigen peptides (MAP) of the P. vivax circumsporozoite protein and 2 with constructs of the P. falciparum merozoite surface protein-1 (MSP-1). The other 2 monkeys served as non-immunized controls. PBMC were cultured for 24 h after stimulation with phytohemagglutinin mitogen, MAP, and MSP-1 antigens. Elevated expression of interleukin-6 (IL-6), IL-10, IL-12, tumor necrosis factor-.alpha. (TNF-.alpha.), TNF-.beta., and iNOS was seen in response to the MAP. Monkeys immunized with either P. falciparum MSP r190L or synthetic 190L peptides expressed predominantly the type-1 cytokines (IL-1.beta., IL-12, interferon-.gamma., TNF-.alpha., TNF-.beta.) characteristic of splenic, cell-mediated activity with macrophage activation and nitric oxide prodn.
 CC 15-5 (Immunochemistry)

IT Aotus
Gene expression
Malaria **vaccines**
Plasmodium falciparum
Plasmodium vivax
(cytokine genes expression in Aotus monkeys immunized with synthetic and recombinant Plasmodium vivax and P. falciparum antigens)

IT **Interleukin 12**
RL: MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)
(cytokine genes expression in Aotus monkeys immunized with synthetic and recombinant Plasmodium vivax and P. falciparum antigens)

IT **10102-43-9, Nitrogen oxide (NO), biological studies**
83869-56-1, GM-CSF
RL: MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)
(cytokine genes expression in Aotus monkeys immunized with synthetic and recombinant Plasmodium vivax and P. falciparum antigens)

IT **125978-95-2, Nitric oxide synthase**
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(inducible; cytokine genes expression in Aotus monkeys immunized with synthetic and recombinant Plasmodium vivax and P. falciparum antigens)

L37 ANSWER 23 OF 25 HCAPLUS COPYRIGHT 2001 ACS

AN 1997:696638 HCAPLUS

DN 128:727

TI DHEA combination therapy with interleukin antibodies for antiviral, antibacterial, antimycoplasmal, or anti-intracellular parasite therapy

IN Prendergast, Patrick T.

PA Prendergast, Patrick T., Ire.

SO PCT Int. Appl., 37 pp.

CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9738695	A1	19971023	WO 1997-IB414	19970417
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	CA 2251733	AA	19971023	CA 1997-2251733	19970417
	AU 9725741	A1	19971107	AU 1997-25741	19970417
	EP 901375	A1	19990317	EP 1997-917365	19970417
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
	CN 1216470	A	19990512	CN 1997-193912	19970417
	JP 2000508654	T2	20000711	JP 1997-536909	19970417
	WO 9847516	A1	19981029	WO 1997-EP5716	19971016
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ,				

PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG,
 US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
 RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR,
 GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA,
 GN, ML, MR, NE, SN, TD, TG

AU 9852219 A1 19981113 AU 1998-52219 19971016
 NO 9804851 A 19981217 NO 1998-4851 19981016

PRAI US 1996-15695 19960417
 WO 1970-IB414 19970417
 WO 1997-IB414 19970417
 WO 1997-EP5716 19971016

OS MARPAT 128:727

AB There are provided medicaments, methods of making them, and kits, which include (1) a 17-ketosteroid compd. and/or (2) anti-serum either poly- or monoclonal to Interleukin 10, Interleukin 2, or Interleukin 12, or with any compd. which can effectively inhibit synthesis or the biol. function of Interleukin 10, Interleukin 12, or Interleukin 2, or with an Interleukin 10, Interleukin 12, or Interleukin 2 receptor mol.-blocking agent, or with anti-serum, either polyclonal or monoclonal to human .alpha.-fetoprotein. There are also provided methods of treatment involving such compds. or combinations of compds., including enhancing

Th1 immune protective responses when using the 17-ketosteroid compd. as an anti-viral, anti-bacterial, anti-mycoplasma or anti-intracellular parasitic agent.

IC ICM A61K031-565
 ICS A61K031-70

CC 2-4 (Mammalian Hormones)
 Section cross-reference(s): 1, 15, 63

IT AIDS (disease)
 Antibacterial agents
 Antiserums
 Antitumor agents
 Antiviral agents
 Human immunodeficiency virus
 Immunological diseases
 Immunosuppressants
 Metastasis inhibitors
 Multiple sclerosis
 Th2 cell
Vaccines
 (DHEA combination therapy with interleukin antibodies for antiviral, antibacterial, antimycoplasmal, or anti-intracellular parasite therapy)

IT **Interleukin 12**
 RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (antibodies to; DHEA combination therapy with interleukin antibodies for antiviral, antibacterial, antimycoplasmal, or anti-intracellular parasite therapy)

IT **Interleukin 12**
 RL: BSU (Biological study, unclassified); BIOL (Biological study) (receptors, blockers; DHEA combination therapy with interleukin antibodies for antiviral, antibacterial, antimycoplasmal, or anti-intracellular parasite therapy)

IT 53-43-0, Dhea 446-72-0, Genistein 2219-31-0, L-Canavanine sulfate

14402-89-2, Sodium nitroprusside 17035-90-4, **L-NMMA**
 35287-69-5, Secalonic acid d 70563-58-5, Herbimycin A
 RL: BAC (Biological activity or effector, except adverse); THU
 (Therapeutic use); BIOL (Biological study); USES (Uses)
 (DHEA combination therapy with interleukin antibodies for antiviral,
 antibacterial, antimycoplasmal, or anti-intracellular parasite
 therapy)

L37 ANSWER 24 OF 25 HCAPLUS COPYRIGHT 2001 ACS
 AN 1997:333720 HCAPLUS
 DN 127:3837
 TI Cellular immune reactions directed against *Toxoplasma gondii* with special
 emphasis on the central nervous system
 AU Daeubener, Walter; Hadding, Ulrich
 CS Institut fur Med. Mikrobiologie und Virologie,
 Heinrich-Heine-Universitat,
 Dusseldorf, Dusseldorf, D-40001, Germany
 SO Med. Microbiol. Immunol. (1997), 185(4), 195-206
 CODEN: MMIYAO; ISSN: 0300-8584
 PB Springer
 DT Journal; General Review
 LA English
 AB A review with 133 refs. *Toxoplasma gondii* is an obligate intracellular
 parasite which, after primary infection of humans, is maintained in a
 dormant state by the host cellular immune system. In the event of an
 acquired immunosuppression, those parasites surviving as dormant cysts in
 the host may undergo a change in status, proliferate and cause a
 life-threatening toxoplasmic encephalitis. Over the last decade much
 knowledge has accumulated concerning the immune response against *T.*
gondii. This review focuses attention particularly on the anti-parasitic
 effector mechanisms and the cellular immune reactions in the central
 nervous system during the course of reactivated toxoplasmic encephalitis.

CC 15-0 (Immunochemistry)
 Section cross-reference(s): 14

IT Interferon .beta.
 Interferon .gamma.
 Interleukin 1
 Interleukin 10
Interleukin 12
 Interleukin 2
 Interleukin 4
 Interleukin 7
 Tumor necrosis factor .alpha.
 RL: BAC (Biological activity or effector, except adverse); BIOL
 (Biological study)
 (cytokines and immunocytes in defense against toxoplasmic
 encephalitis)

IT **10102-43-9, Nitric oxide**, biological studies
 83869-56-1, Granulocyte-macrophage colony-stimulating factor
 RL: BAC (Biological activity or effector, except adverse); BIOL
 (Biological study)
 (cytokines and **immunocytes** in defense against toxoplasmic
 encephalitis)

L37 ANSWER 25 OF 25 HCAPLUS COPYRIGHT 2001 ACS
 AN 1996:659868 HCAPLUS
 DN 125:299294

TI **IL-12** enhances **vaccine**-induced immunity to schistosomes by augmenting both humoral and cell-mediated immune responses against the parasite

AU Wynn, Thomas A.; Reynolds, Alicia; James, Stephanie; Cheever, Allen W.; Caspar, Pat; Hieny, Sara; Jankovic, Dragana; Strand, Mette; Sher, Alan

CS Immunobiol. Section, Natl. Inst. Health, Bethesda, MD, 20892, USA

SO J. Immunol. (1996), 157(9), 4068-4078
CODEN: JOIMA3; ISSN: 0022-1767

DT Journal

LA English

AB The prodn. of Th1-type cytokines is assocd. with strong cell-mediated immunity, while Th2-type cytokines typically dominate humoral immune responses. In mice vaccinated a single time with attenuated cercariae of *Schistosoma mansoni*, the protection induced is assocd. with Th1 cytokine-dependent, cell-mediated immunity. In contrast, mice vaccinated multiple times display a more Th2-type dominant cytokine response and develop Ab-dependent resistance. We have previously shown that IL-12 enhances cell-mediated immunity in singly vaccinated mice. In the present study, we asked what effects administering IL-12 as an adjuvant would have on the development of a protective humoral response in multiply immunized animals. We found that multiply immunized/IL-12-treated mice displayed a marked increase in resistance to challenge infection, with some animals demonstrating complete protection. The IL-12-vaccinated mice developed strongly polarized Th1 responses but, importantly, also showed significant increases in parasite-specific Ab and, in particular, IgG2a, IgG2b, and IgG1 isotypes. Passive transfer demonstrated an enhanced ability of serum from these animals to protect naive recipients. In addn., animals vaccinated in the presence of IL-12 also developed macrophages with increased nitric oxide-dependent killing activity against the parasites. Together, these data demonstrate that IL-12, initially described as an adjuvant for cell-mediated immunity, may be used to simultaneously promote both humoral and cell-mediated protective responses against infection.

CC 15-8 (Immunochemistry)

ST *Schistosoma* infection immunity **interleukin 12**

IT Lymphokines and Cytokines
RL: MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)
(**interleukin-12** enhances cytokine formation by T-cells in relation to immunity to schistosomes)

IT Macrophage
(**interleukin-12** enhances **nitric oxide**-dependent killing of schistosomes by macrophages)

IT *Schistosoma mansoni*
Vaccines
(**interleukin-12** enhances **vaccine**-induced immunity to schistosomes by augmenting both humoral and cell-mediated immune responses against the parasite)

IT Antibodies
RL: MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)
(**interleukin-12** enhances **vaccine**-induced

- immunity to schistosomes by augmenting both humoral and cell-mediated immune responses against the parasite)
- IT Lymphocyte
(T-cell, helper cell/inducer, TH1, **interleukin-12**
enhances **vaccine**-induced immunity to schistosomes by
augmenting both humoral and cell-mediated immune responses against the
parasite)
- IT Lymphokines and Cytokines
RL: BAC (Biological activity or effector, except adverse); BIOL
(Biological study)
(**interleukin 12, interleukin-12**
enhances **vaccine**-induced immunity to schistosomes by
augmenting both humoral and cell-mediated immune responses against the
parasite)
- IT 10102-43-9, **Nitric oxide**, biological studies
RL: BAC (Biological activity or effector, except adverse); MFM (Metabolic
formation); BIOL (Biological study); FORM (Formation, nonpreparative)
(**interleukin-12** enhances **nitric**
oxide-dependent killing of schistosomes by macrophages)

W: AE AG AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM DZ
 EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK
 LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI
 SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW

ADT WO 2000066720 A2 WO 2000-US11356 20000428

PRAI US 1999-132123 19990430

AB WO 200066720 A UPAB: 20001230

NOVELTY - Protecting pancreatic islet beta -cells from immune system-mediated toxicity comprises transducing the pancreatic islet beta -cells with adeno-associated virus (AAV) vectors into which are inserted genetic materials that encode products that reduce immune system-mediated cell toxicity in the transduced cells.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) AAV vectors into which are inserted pancreatic islet beta-cell cytoprotective genetic materials; and

(2) preventing rejection of transplanted pancreatic islet beta-cells.

ACTIVITY - Immunosuppressive; antidiabetic.

MECHANISM OF ACTION - Gene therapy; cytoprotective.

No supporting biological data given.

USE - To protect pancreatic islet beta -cells from immune system-mediated toxicity and to prevent rejection of transplanted pancreatic islet beta -cells (claimed). The vectors can be used in gene therapy and also to prevent the development of type I diabetes.

ADVANTAGE - AAV is non-pathogenic because it requires co-infection with a helper virus for productive infection, but does not require co-infection to become integrated into a host cell or to persist in host cells, thus leading to long-term, stable gene expression, even in the non-dividing cells pancreatic beta -cells. The AAV vectors may integrate as multi-copy tandem repeats, unlike retroviral vectors, thus enhancing transgene expression. The small genome of AAV allows for early manipulation by standard recombinant methodology. The use of AAV transduction is advantageous in that DNA polymerase, the enzyme responsible for AAV replication, has a 10,000-fold lower error rate than reverse transcriptase.

Dwg.0/6

L9 ANSWER 2 OF 5 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD

AN 2000-452382 [39] WPIDS

DNC C2000-137931

TI Expression vector comprising multiple shear stress response elements, useful for modulating endothelial cell proliferation, stimulating or down-regulating angiogenesis and treating vasculogenic/angiogenic disorders.

DC B04 D16

IN RESNICK, N

PA (FLOR-N) FLORENCE MEDICAL LTD

CYC 90

PI WO 2000039275 A2 20000706 (200039)* EN 61p

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL
 OA PT SD SE SL SZ TZ UG ZW

W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM EE ES
 FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS
 LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL
 TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW

AU 2000017954 A 20000731 (200050)

ADT WO 2000039275 A2 WO 1999-IL702 19991223; AU 2000017954 A AU 2000-17954 19991223

FDT AU 2000017954 A Based on WO 200039275

PRAI US 1998-220510 19981224; US 1998-113863 19981224

AB WO 200039275 A UPAB: 20000818

NOVELTY - A vector (I) comprising a multiple number of nucleic acids of promoter Shear Stress Response Elements (SSRE) and one or more genes, or

a nucleic acid of an antisense molecule, ribozyme, double stranded RNA, or

a nucleic acid which encodes for a repressor antibody, mutant protein which inhibits the synthesis of, or activity of the protein or peptide, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

- (1) a host cell comprising (I); and
- (2) a method for screening (III) test compound for their ability to regulate angiogenesis and/or vasculogenesis, comprising:
 - (a) contacting endothelial cells with the compound to be tested;
 - (b) assaying the amount of angiogenesis and/or vasculogenesis produced as a result of the test compound;
 - (c) stimulating endothelial cells by introducing (I);
 - (d) assaying the amount of angiogenesis and/or vasculogenesis produced as a result of the vector;
 - (e) comparing the amount of angiogenesis and/or vasculogenesis produced as a result of (b) to that of (d), where an increased amount of angiogenesis and/or vasculogenesis of the test compound indicates that

the test compound regulates angiogenesis and/or vasculogenesis.

ACTIVITY - Cytostatic; Cardiant; Vasotropic; Vulnerary; Antidiabetic;

Antiatherosclerotic; Hypotensive; Antilipemic.

MECHANISM OF ACTION - Gene therapy.

No supporting biological data is provided.

USE - (I) is useful for stimulating or inhibiting vascular endothelial cell or capillary endothelial cell proliferation and for stimulating angiogenesis in cells. (I) or (II) is useful for modulating vascular permeability in a mammal, for stimulating or inhibiting the formation, maturation or regression of blood vessels, modulating genes or proteins involved in a diseases, down regulating angiogenesis and for treating vasculogenic and/or angiogenic disorders. These disorders include

cardiovascular disorder, neoplastic disorders, ischemia, atherosclerosis, hypertension, diabetes, hypercholesterolemia and wound healing.

(II) is administered to the mammal in the vasculature such that the vasculature has shear stress forces to permit SSRE to be activated by the shear stress and transcriptionally regulate endothelial cell gene expression. Down regulation of angiogenesis further comprises administering an inflammatory agent, vasodilator, fibrinolytic

activators, tumor necrosis factor (TNF) or thrombotic factors or an agent which acts as a vasoconstrictor.

(I) is also useful for detecting shear stress or shear stress related

condition in a subject, where the reporter gene in (I) is activated in shear stress environment indicating shear stress or its related condition.

SSRE vectors are also useful for screening test compounds for their

ability to regulate angiogenesis and/or vasculogenesis (all claimed).
Dwg.0/2

L9 ANSWER 3 OF 5 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
AN 2000-224531 [19] WPIDS
DNC C2000-068615
TI Method of inhibiting injury to vascular tissue comprising local
administration of antiangiogenic agent.
DC B05 D16
IN BROWN, C L; GORLIN, S
PA (GLOB-N) GLOBAL VASCULAR CONCEPTS INC
CYC 87
PI WO 2000010552 A2 20000302 (200019)* EN 29p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL
OA PT SD SE SL SZ UG ZW
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM EE ES
FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS
LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ
TM TR TT UA UG UZ VN YU ZA ZW
AU 9956871 A 20000314 (200031)
ADT WO 2000010552 A2 WO 1999-US19218 19990824; AU 9956871 A AU 1999-56871
19990824
FDT AU 9956871 A Based on WO 200010552
PRAI US 1998-97579 19980824
AB WO 200010552 A UPAB: 20000419
NOVELTY - A new method of inhibiting injury to vascular tissue comprises
local administration of an anti-angiogenic agent.
ACTIVITY - Antiarteriosclerosis; cardiant; vasotropic; antianginal,
cerebroprotective; cytostatic.
MECHANISM OF ACTION - None given.
USE - The vascular injury is due to atherosclerosis, cardiac
transplant vasculopathy, coronary restenosis following coronary
intervention, balloon angioplasty, stent placement, rotablator, carotid
endarterectomy, dialysis graft stenosis, graft anastomosis neointima,
unstable angina, acute myocardial infarction, stroke, benign hypertrophy
or benign prostatic hypertrophy, particularly atherosclerosis or
restenosis.
Dwg.0/6

L9 ANSWER 4 OF 5 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
AN 1999-243663 [20] WPIDS
DNC C1999-071033
TI Method for inducing a protective mucosal cytotoxic T lymphocyte immune
response.
DC A96 B04 D16
IN BELYAKOV, I M; BERZOFSKY, J A; DERBY, M A; KELSALL, B L; STROBER, W
PA (USSH) US DEPT HEALTH & HUMAN SERVICES; (USSH) US DEPT HEALTH & HUMAN
SERVICE
CYC 83
PI WO 9912563 A2 19990318 (199920)* EN 85p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL
OA PT SD SE SZ UG ZW
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE
GH GM HR HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG
MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG
US UZ VN YU ZW
AU 9893862 A 19990329 (199932)

EP 1011720 A2 20000628 (200035) EN
 R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
 ADT WO 9912563 A2 WO 1998-US19028 19980911; AU 9893862 A AU 1998-93862
 19980911; EP 1011720 A2 EP 1998-946965 19980911, WO 1998-US19028 19980911
 FDT AU 9893862 A Based on WO 9912563; EP 1011720 A2 Based on WO 9912563
 PRAI US 1998-74894 19980217; US 1997-58523 19970911
 AB WO 9912563 A UPAB: 19990525

NOVELTY - A novel method for inducing a protective mucosal cytotoxic T lymphocyte (CTL) response in a mammalian subject comprises contacting a mucosal tissue of the subject with a composition comprising a purified soluble antigen.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for:

(1) a method for inducing a protective mucosal CTL response in a subject comprising contacting a mucosal tissue of the subject with a composition comprising a soluble antigen which does not comprise an adjuvant; and

(2) an immunogenic composition for inducing a protective mucosal CTL response in a subject and adapted for intrarectal administration comprising a purified soluble antigen formulated for intrarectal delivery to the rectum, colon, sigmoid colon or distal colon.

USE - The methods can induce a protective mucosal CTL response in a subject. The method can be used for protection against e.g. hepatitis A virus, papilloma virus, feline immunodeficiency virus, feline leukemia virus, *Listeria monocytogenes*, *M. tuberculosis*, *M. leprae*, or *Giardia lamblia*.

ADVANTAGE - The method induces long-lasting protective mucosal immune responses.
 Dwg.0/17

L9 ANSWER 5 OF 5 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
 AN 1998-348525 [30] WPIDS
 DNC C1998-107826
 TI New method for treating or preventing asthma - comprises use of DNA encoding IFN-gamma, IL-10, IL-12 or nitric oxide synthase and DNA for control of expression using a ligand.
 DC B04 D16
 IN CERASOLI, F
 PA (ARIA-N) ARIAD GENE THERAPEUTICS INC
 CYC 23
 PI WO 9826066 A1 19980618 (199830)* EN 63p
 RW: AT BE CH DE DK ES FI FR GB GR IE IT LU MC NL PT SE
 W: AU CA JP KR US
 AU 9878476 A 19980703 (199847)
 EP 948619 A1 19991013 (199947) EN
 R: AT BE CH DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
 ADT WO 9826066 A1 WO 1997-US22454 19971209; AU 9878476 A AU 1998-78476
 19971209; EP 948619 A1 EP 1997-949785 19971209, WO 1997-US22454 19971209
 FDT AU 9878476 A Based on WO 9826066; EP 948619 A1 Based on WO 9826066
 PRAI US 1996-32260 19961209
 AB WO 9826066 A UPAB: 19991122
 A method for treating or preventing asthma in a mammal comprising genetically engineered cells, comprises administering to the mammal a ligand. The cells comprise: (a) at least one target DNA construct containing a target gene encoding interferon (IFN)- gamma , interleukin (IL)-10, IL-12 or nitric oxide (NO) synthase operably linked to a heterologous

transcription control element, and (b) at least one DNA construct encoding

a transcription regulating protein, which, in the presence of a ligand to which it binds, activates expression of the target gene. Also claimed are:

(1) a method for genetically engineering mammalian cells, to render them capable of regulated expression of a target gene comprising a DNA sequence

encoding a target protein selected from IFN- gamma , IL-10, IL-12, and NO synthase, comprising introducing into the cells a target DNA construct comprising a target gene linked to a

transcription control sequence permitting ligand-dependent expression of the target gene, and (2) a method for genetically engineering mammalian cells, to render them capable of ligand dependent expression of a target protein, comprising introducing into the cells: (a) a first DNA construct encoding a chimeric protein comprising: (i) at least one receptor domain capable of binding to the ligand, and (ii) a signal initiation domain, heterologous with respect to the receptor domain, but capable, upon oligomerisation with at least 1 other like domains, of triggering the activation of transcription of a target gene under the transcription control of a transcription control element responsive to the oligomerisation, and (b) a target gene construct comprising a gene encoding a target protein under the expression control of a transcription control element responsive to the oligomerisation; and which following exposure to the ligand, expresses the target gene.

USE - Asthma has been defined as a lung disease characterised by: (i)

reversible (not completely in some patients) airway obstruction either spontaneously or with treatment; (ii) airway inflammation, and (iii) increased airway responsiveness to a variety of stimuli. Asthma also has been defined as a chronic inflammatory disorders of the airways in which many cells play a role, including mast cells and eosinophils. In susceptible individuals the inflammation causes symptoms usually associated with widespread but variable airflow obstruction. So, the method can be used for treating or preventing asthma and related disorders.

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E NITRIC OXIDE/CN
L1 1 S E3
E NITRIC OXIDE SYNTHASE/CN
L2 1 S E3
E L-NAME/CN
L3 1 S E3
E L-NMMA/CN
L4 1 S E3
L5 4 S L1 OR L2 OR L3 OR L4

FILE 'BIOSIS' ENTERED AT 10:42:26 ON 22 FEB 2001
L6 51756 S L5
L7 59656 S L6 OR NITRIC OXIDE OR NO SYNTHASE OR L NAME OR L NMMA
L8 5921 S INTERLEUKIN 12 OR IL12 OR IL 12
L9 254 S L8 AND L7
L10 33309 S ADJUVANT#
L11 62517 S VACCINE#
L12 10 S L10 AND L9
L13 0 S TI 1-10
L14 4726 S L8/IT
L15 203 S L14 AND L7
L16 8 S L15 AND L10
L17 10 S L15 AND L11
L18 15786 S IMMUNOSTIMU? OR IMMUN? (2A) STIMUL?
L19 11 S L18 AND L15
L20 24 S L19 OR L17 OR L16
L21 7652 S L3 OR L4 OR L NAME OR L NMMA
L22 7 S L21 AND L8
L23 7 S L22 NOT L20

FILE 'BIOSIS' ENTERED AT 10:51:52 ON 22 FEB 2001

=> d bib ab it l20 1-24;d bib ab it l23 1-7

L20 ANSWER 1 OF 24 BIOSIS COPYRIGHT 2001 BIOSIS
 AN 2001:84465 BIOSIS
 DN PREV200100084465
 TI Effects of cholera toxin on macrophage production of co-stimulatory cytokines.
 AU Cong, Yingzi; Oliver, Alfred O.; Elson, Charles O. (1)
 CS (1) Division of Gastroenterology and Hepatology, University of Alabama at Birmingham, 703 S. 19th Street, 633 Zeigler Research Building, Birmingham, AL, 35294-0007: charles-elson@gihep.uab.edu USA
 SO European Journal of Immunology, (January, 2001) Vol. 31, No. 1, pp. 64-71.
 print.
 ISSN: 0014-2980.
 DT Article
 LA English
 SL English
 AB Cholera toxin (CT), the enterotoxin of *Vibrio cholerae*, is a potent mucosal and systemic immunogen and **adjuvant**. The precise mechanism of the adjuvanticity of CT is poorly understood. Our previous work has showed that CT up-regulates B7.2, but not B7.1 expression on macrophages, and thus increases their co-stimulatory activity. In the current study, the effects of CT on macrophage co-stimulatory cytokine production were investigated. Bone marrow macrophages were generated by culturing bone marrow cells with macrophage colony-stimulating factor. CT treatment increased endotoxin-stimulated macrophage IL-10, IL-6, and IL-1beta production, whereas it decreased IL-12, TNF-alpha and **nitric oxide** production. Antibody blocking experiments showed that CT inhibition of IL-12 and TNF-alpha production was mediated by increased IL-10 production, in that addition of anti-IL-10 monoclonal antibody abrogated CT inhibition. The decrease in **nitric oxide** production was in turn secondary to inhibition of TNF-alpha production. Taken together, our study demonstrated that CT has differential effects on various macrophage co-stimulatory cytokines, effects that are likely to contribute to its adjuvanticity.
 IT Major Concepts
 Immune System (Chemical Coordination and Homeostasis); Infection
 IT Parts, Structures, & Systems of Organisms
 bone marrow: blood and lymphatics, immune system; macrophage: blood and lymphatics, immune system, production
 IT Chemicals & Biochemicals
 IL-1-beta [interleukin-1-beta]: production; IL-10 [interleukin-10]: production; **IL-12 [interleukin-12]**: production; IL-6 [interleukin-6]: production; TNF-alpha [tumor necrosis factor-alpha]: production; cholera toxin: **adjuvant**, enterotoxin, immunogen; macrophage colony-stimulating factor; **nitric oxide**: production
 ORGN Super Taxa
 Animalia; Vibrionaceae: Facultatively Anaerobic Gram-Negative Rods, Eubacteria, Bacteria, Microorganisms
 ORGN Organism Name
 Vibrio cholerae (Vibrionaceae): pathogen; animal (Animalia)
 ORGN Organism Superterms
 Animals; Bacteria; Eubacteria; Microorganisms
 RN 81627-83-0 (MACROPHAGE COLONY-STIMULATING FACTOR)
 10102-43-9 (NITRIC OXIDE)

L20 ANSWER 2 OF 24 BIOSIS COPYRIGHT 2001 BIOSIS
 AN 2001:50600 BIOSIS
 DN PREV200100050600
 TI Adherent dendritic cells expressing high levels of interleukin-10 and low levels of interleukin-12 induce antigen-specific tolerance to experimental autoimmune encephalomyelitis.
 AU Yang, J.-S.; Xu, L.-Y.; Huang, Y.-M.; Van Der Meide, P. H.; Link, H.; Xiao, B.-G. (1)
 CS (1) Karolinska Institute, Division of Neurology, Huddinge University Hospital, Huddinge, S-141 86, Stockholm Sweden
 SO Immunology, (November, 2000) Vol. 101, No. 3, pp. 397-403. print. ISSN: 0019-2805.
 DT Article
 LA English
 SL English
 AB We have previously shown that tolerance can be induced against acute experimental autoimmune encephalomyelitis (EAE) in Lewis rats by bone marrow-derived dendritic cells (DC) that have been pulsed in vitro with encephalitogenic myelin basic protein peptide 68-86 (MBP 68-86), and injected subcutaneously into healthy rats prior to immunization with MBP 68-86 plus complete Freund's **adjuvant**. To elucidate better the properties of tolerogenic DC, we here compared plastic-adherent DC with floating, non-adherent DC, which were cultured for 7 days in the presence of granulocyte-macrophage colony-stimulating factor plus interleukin-4 (IL-4). Adherent DC expressed high levels of IL-10 mRNA and protein, and low levels of IL-12 mRNA and showed high expression of CD54 compared with floating DC. Proliferation, nitrite concentration and capacity for antigen presentation were lower in adherent DC than in floating DC. There were no differences between adherent and floating DC regarding expression of CD11c, OX62, major histocompatibility complex class II, CD80, or CD86. Most importantly, we observed that adherent DC induced tolerance to EAE in vivo when injected subcutaneously into Lewis rats prior to immunization, while floating DC did not. Adherent DC-mediated tolerance to EAE was associated with augmented proliferation, **nitric oxide** production and frequency of apoptotic cells as well as with up-regulation of transforming growth factor-beta (TGF-beta) -expressing cells in T-cell areas of lymph nodes. Tolerance induction by adherent DC seems to be related to a **nitric oxide**-apoptosis pathway and to upregulation of TGF-beta-expressing cells.
 IT Major Concepts
 Immune System (Chemical Coordination and Homeostasis)
 IT Parts, Structures, & Systems of Organisms
 dendritic cell: immune system
 IT Diseases
 autoimmune encephalomyelitis: immune system disease
 IT Chemicals & Biochemicals
 CD11c; CD54; CD80; CD86; OX62; granulocyte-macrophage colony stimulating factor; interleukin-10; **interleukin-12**; interleukin-4; major histocompatibility complex class II; transforming growth factor-beta
 IT Alternate Indexing
 Encephalomyelitis, Allergic (MeSH)
 ORGN Super Taxa

Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia

ORGN Organism Name
rat (Muridae)

ORGN Organism Superterms
Animals; Chordates; Mammals; Nonhuman Mammals; Nonhuman Vertebrates;
Rodents; Vertebrates

RN 83869-56-1 (GRANULOCYTE-MACROPHAGE COLONY STIMULATING FACTOR)

L20 ANSWER 3 OF 24 BIOSIS COPYRIGHT 2001.BIOSIS

AN 2000:439178 BIOSIS

DN PREV200000439178

TI NOS-2 mediates the protective anti-inflammatory and antifibrotic effects of the Th1-inducing **adjuvant**, IL-12, in a Th2 model of granulomatous disease.

AU Hesse, Matthias; Cheever, Allen W.; Jankovic, Dragana; Wynn, Thomas A.
(1)

CS (1) Laboratory of Parasitic Diseases, NIH/NIAID, Bldg. 7, Room 318, Bethesda, MD, 20892 USA

SO American Journal of Pathology, (September, 2000) Vol. 157, No. 3, pp. 945-955. print.
ISSN: 0002-9440.

DT Article

LA English

SL English

AB Mice sensitized with *Schistosoma mansoni* eggs and IL-12 develop liver granulomas, on subsequent infection, which are esmaller and less fibrotic than those in nonsensitized mice. The protective response is accompanied by a shift in the type-2 cytokine profile to one dominated by type-1 cytokines. The deviated response is associated with marked increases in inducible **nitric oxide** synthase (NOS-2) activity. Here, we demonstrate, by using NOS-2-deficient mice, that the anti-inflammatory and anti-fibrotic effects of the type-1 response are completely NOS-2-dependent. Strikingly, despite developing a polarized type-1 cytokine response that was similar in magnitude, the egg/IL-12-sensitized NOS-deficient mice developed granulomas 8 times larger than WT mice did. There was also no decrease in hepatic fibrosis in the sensitized mutant animals. Interferon-gamma-deficient mice failed to exhibit the exacerbated inflammatory response, despite displaying a marked deficiency in **nitric oxide** production. However, immune deviation was unsuccessful in the latter animals, which suggested that the increase in inflammation in NOS-deficient mice resulted from a polarized but **nitric oxide**-deficient type-1 response. These results reveal a beneficial role for NOS-2 in the regulation of inflammation and suggest that the ultimate success of Th2-to-Th1 immune deviation strategies will rely on the efficient activation of NOS-2 expression in downstream effector cells.

IT Major Concepts
Enzymology (Biochemistry and Molecular Biophysics); Immune System (Chemical Coordination and Homeostasis); Digestive System (Ingestion and Assimilation)

IT Parts, Structures, & Systems of Organisms
Th1 cells: blood and lymphatics, immune system; Th2 cells: blood and lymphatics, immune system

IT Diseases

liver fibrosis: digestive system disease

IT Chemicals & Biochemicals
IL-12 [interleukin-12]:
 antifibrotic, antiinflammatory; **nitric oxide**
 synthase-2 [NOS-2]

IT Alternate Indexing
 Liver Cirrhosis (MeSH)

ORGN Super Taxa
 Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia

ORGN Organism Name
 mouse (Muridae)

ORGN Organism Superterms
 Animals; Chordates; Mammals; Nonhuman Mammals; Nonhuman Vertebrates;
 Rodents; Vertebrates

L20 ANSWER 4 OF 24 BIOSIS COPYRIGHT 2001 BIOSIS

AN 2000:382616 BIOSIS

DN PREV200000382616

TI Interleukin-12 (IL-12) enhancement of the cellular immune response
 against
 human immunodeficiency virus type 1 Env antigen in a DNA prime/vaccinia
 virus boost **vaccine** regimen is time and dose dependent:
 Suppressive effects of IL-12 boost are mediated by **nitric**
oxide.

AU Gherardi, M. Magdalena; Ramirez, Juan C.; Esteban, Mariano (1)

CS (1) Centro Nacional Biotecnologia (CSIC), Campus Cantoblanco, 28049,
 Madrid Spain

SO Journal of Virology, (July, 2000) Vol. 74, No. 14, pp. 6278-6286. print.
 ISSN: 0022-538X.

DT Article

LA English

SL English

AB We previously demonstrated that codelivery of interleukin-12 (IL-12) with
 the human immunodeficiency virus type 1 (HIV-1) Env antigen from a
 recombinant vaccinia virus (rVV) can enhance the specific anti-Env
 cell-mediated immune (CMI) response. In the present study, we have
 investigated the effects of IL-12 in mice when it is expressed in a DNA
 prime/VV boost **vaccine** regimen. The delivery of IL-12 and Env
 product during priming with a DNA vector, followed by a booster with VV
 expressing the Env gene (rVVenv), was found to trigger the optimal CMI
 response compared with other immunization schedules studied.
 Significantly, if IL-12 is also delivered as a booster from the viral
 vector, an impairment of the effects of IL-12 was observed involving
nitric oxide (NO), since it was overcome by specific
 inhibitors of inducible **NO synthase**. NO caused
 transient immunosuppression rather than impairment of viral replication.
 Moreover, at certain viral doses, coadministration of the NO inhibitor
 during the booster resulted in IL-12-mediated enhancement of the specific
 CD8+ T-cell response. In addition, the dose of the IL-12-encoding plasmid
 (pIL-12) and the route of administration of both vectors were relevant
 factors for optimal CMI responses. Maximal numbers of Env-specific CD8+
 gamma interferon-secreting cells were obtained when 50 mug of pIL-12 was
 administered intramuscularly at priming, followed by an intravenous
 rVVenv
 boost. Our results demonstrate, in a murine model, critical parameters
 affecting the success of vaccination schedules based on a combination of
 DNA and VV vectors in conjunction with immunomodulators.

IT Major Concepts
 Immune System (Chemical Coordination and Homeostasis); Pharmacology

IT Parts, Structures, & Systems of Organisms
 CD8-positive T cell

IT Chemicals & Biochemicals
 DNA prime/vaccina virus boost **vaccine**:
immunostimulant - drug; Env: antigen; gamma interferon;
 immunomodulator; **interleukin-12** [IL-
 12]: boost, suppressive effects; **nitric oxide**
 ; **nitric oxide** synthase; pIL-12: plasmid

IT Miscellaneous Descriptors
 CD8-positive T cell response; cellular immune response: enhancement

ORGN Super Taxa
 Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia;
 Retroviridae: Animal Viruses, Viruses, Microorganisms

ORGN Organism Name
 human immunodeficiency virus type 1 [HIV-1] (Retroviridae): pathogen;
 mouse (Muridae): animal model, host

ORGN Organism Superterms
 Animal Viruses; Animals; Chordates; Mammals; Microorganisms; Nonhuman
 Mammals; Nonhuman Vertebrates; Rodents; Vertebrates; Viruses

RN 10102-43-9 (NITRIC OXIDE)
 125978-95-2 (NITRIC OXIDE SYNTHASE)

L20 ANSWER 5 OF 24 BIOSIS COPYRIGHT 2001 BIOSIS

AN 2000:377239 BIOSIS

DN PREV200000377239

TI Direct stimulation of macrophages by IL-12 and IL-18: A bridge too far.

AU Golab, Jakub (1); Zagozdzon, Radoslaw; Stoklosal, Tomasz; Kaminski,
 Rafal;
 Kozar, Katarzyna; Jakobisiak, Marek

CS (1) Department of Immunology, Institute of Biostructure, Medical
 University of Warsaw, ul. Chalubinskiego 5, 02-004, Warsaw Poland

SO Immunology Letters, (June 1, 2000) Vol. 72, No. 3, pp. 153-157. print.
 ISSN: 0165-2478.

DT Article

LA English

SL English

AB A novel pathway of autocrine macrophage activation based on a positive
 feedback loop involving interleukin (IL)-12, IL-18 and IFN-gamma has
 recently been suggested. However, the macrophage isolation technique
 employed to describe the above phenomenon does not allow obtaining a pure
 population of macrophages casting some doubt to its existence. In the
 present study, we show that even minor contamination with lymphoid cells
 of a pure population of macrophage-like cells (Raw 264.7) results in a
 marked production of **nitric oxide** after stimulation
 with both IL-12 and IL-18. Neither macrophage-like cells nor lymphoid
 cells were capable of secreting high amounts of **nitric**
oxide after stimulation with IL-12 and/or IL-18. Based on these
 observations we hypothesize that proposed autocrine feedback loop of
 macrophage activation is rather paracrine in nature and involves direct
 stimulation of residual lymphoid cells to secrete IFN-gamma that is then
 capable of activating macrophages.

IT Major Concepts
 Immune System (Chemical Coordination and Homeostasis)

IT Parts, Structures, & Systems of Organisms
 lymphoid cell: blood and lymphatics, immune system; macrophage: blood

and lymphatics, direct **stimulation**, **immune** system

IT Chemicals & Biochemicals
interferon-gamma; **interleukin-12**; interleukin-18

IT Miscellaneous Descriptors
positive feedback loop

ORGN Super Taxa
Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia

ORGN Organism Name
Raw 264.7 cell line (Muridae): murine macrophage-like cell

ORGN Organism Superterms
Animals; Chordates; Mammals; Nonhuman Mammals; Nonhuman Vertebrates;
Rodents; Vertebrates

L20 ANSWER 6 OF 24 BIOSIS COPYRIGHT 2001 BIOSIS

AN 2000:216872 BIOSIS

DN PREV200000216872

TI Tumor necrosis factor is required for the priming of peritoneal macrophages by trehalose dimycolate.

AU Oswald, Isabelle P.; Dozois, Charles M.; Fournout, Sylvie; Petit, Jean-Francois; Lemaire, Genevieve (1)

CS (1) UMR CNRS 8619, Universite Paris-Sud, Batiment 430, 91405, Orsay Cedex France

SO European Cytokine Network, (Dec., 1999) Vol. 10, No. 4, pp. 533-540. ISSN: 1148-5493.

DT Article

LA English

SL English

AB Trehalose dimycolate (TDM), a glycolipid present in the cell wall of Mycobacterium spp., is a powerful **immunostimulant**. We have developed an original model of macrophage activation where TDM is injected in vivo to prime peritoneal macrophages. These primed macrophages do not express inducible **NO synthase** (NOS II), however, they can be fully activated, i. e. induced to express NOS II and to develop a NOS II-dependent antiproliferative activity, following in vitro exposure to low concentrations of LPS. In a previous paper, we have shown that TDM-priming of mouse peritoneal macrophages is mediated by the sequential production of IL-12 and IFN-gamma. In the present paper, we investigated the role of TNF in the priming of macrophages by TDM. By semi-quantitative RT-PCR, we have shown that TDM injection induced transcription of TNF-alpha in peritoneal cells. TNF-mRNA levels peaked 5 hours after TDM injection and remained elevated for at least 32 hours. TNF expression was absolutely necessary for macrophage priming, as injection of an anti-TNF monoclonal antibody, 4 h before and 20 hours after TDM injection, prevented LPS-dependent activation of macrophages in vitro. This result was confirmed by the inability of TDM to prime macrophages from LT-alpha/TNF-alpha knockout (LT/TNFKO) mice. In addition, analysis of LT/TNFKO mice treated with TDM revealed that induction of the IL-12 transcript in their peritoneal cells and expression of a functional NADPH oxidase in macrophages are TNF-independent events.

IT Major Concepts
Immune System (Chemical Coordination and Homeostasis)

IT Parts, Structures, & Systems of Organisms
peritoneal macrophage: blood and lymphatics, immune system, primed

IT Chemicals & Biochemicals
IFN-gamma [interferon-gamma]; IL-12 [

interleukin-12]: transcription; NADPH oxidase;
 TNF-alpha [tumor necrosis factor-alpha]: expression, transcription;
 cytokine; **nitric oxide** synthase; trehalose
 dimycolate: **immunostimulant**, mycobacterial glycolipid

ORGN Super Taxa
 Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia;
 Mycobacteriaceae: Mycobacteria, Actinomycetes and Related Organisms,
 Eubacteria, Bacteria, Microorganisms

ORGN Organism Name
 Mycobacterium spp. (Mycobacteriaceae); mouse (Muridae)

ORGN Organism Superterms
 Animals; Bacteria; Chordates; Eubacteria; Mammals; Microorganisms;
 Nonhuman Mammals; Nonhuman Vertebrates; Rodents; Vertebrates

RN 9032-22-8Q (NADPH OXIDASE)
 37256-37-4Q (NADPH OXIDASE)
 125978-95-2 (**NITRIC OXIDE** SYNTHASE)

L20 ANSWER 7 OF 24 BIOSIS COPYRIGHT 2001 BIOSIS
 AN 2000:216862 BIOSIS
 DN PREV200000216862
 TI **Immunostimulatory** DNA is a potent agonist of IL-12, IFNgamma and
nitric oxide production by skin macrophages from
 Leishmania-susceptible mice.
 AU von Stebut, E. (1); Udey, M. (1)
 CS (1) Dermatology Branch, NCI, Bethesda, MD USA
 SO Journal of Investigative Dermatology, (April, 2000) Vol. 114, No. 4, pp.
 798.
 Meeting Info.: 61st Annual Meeting of the Society for Investigative
 Dermatology. Chicago, Illinois, USA May 10-14, 2000
 ISSN: 0022-202X.

DT Conference
 LA English
 SL English
 IT Major Concepts
 Endocrine System (Chemical Coordination and Homeostasis);
 Integumentary
 System (Chemical Coordination and Homeostasis)
 IT Parts, Structures, & Systems of Organisms
 skin macrophage: blood and lymphatics, immune system
 IT Chemicals & Biochemicals
 DNA; IFN-gamma [interferon-gamma]; **IL-12** [
interleukin-12]; **nitric oxide**:
 production
 IT Miscellaneous Descriptors
 Meeting Abstract

ORGN Super Taxa
 Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia

ORGN Organism Name
 mouse (Muridae): BALB/C, Leishmania-susceptible

ORGN Organism Superterms
 Animals; Chordates; Mammals; Nonhuman Mammals; Nonhuman Vertebrates;
 Rodents; Vertebrates

RN 10102-43-9 (**NITRIC OXIDE**)

L20 ANSWER 8 OF 24 BIOSIS COPYRIGHT 2001 BIOSIS
 AN 2000:49297 BIOSIS
 DN PREV200000049297

TI Vasoactive intestinal peptide and pituitary adenylate cyclase-activating polypeptide inhibit interleukin-12 transcription by regulating nuclear factor kappaB and Ets activation.

AU Delgado, Mario; Ganea, Doina (1)

CS (1) Dept. Biological Sciences, Rutgers Univ., 101 Warren St., Newark, NJ USA

SO Journal of Biological Chemistry, (Nov. 5, 1999) Vol. 274, No. 45, pp. 31930-31940.
ISSN: 0021-9258.

DT Article

LA English

SL English

AB The vasoactive intestinal peptide (VIP) and the structurally related neuropeptide pituitary adenylate cyclase-activating polypeptide (PACAP) act as "macrophage-deactivating factors". We showed previously that VIP and PACAP inhibit the production of macrophage-derived tumor necrosis factor-alpha, interleukin (IL)-6, **nitric oxide**, and IL-12. This study examines the molecular mechanisms involved in the VIP/PACAP inhibition of IL-12 production. VIP and PACAP inhibit IL-12 (p40) gene expression by affecting both NF-kappaB binding and the composition of the Ets-2 binding complex. Both neuropeptides prevent the activation-induced nuclear translocation of the NF-kappaB components p65 and c-Rel by inhibiting the reduction in cytoplasmic IkappaBalpha. Moreover, VIP and PACAP inhibit the synthesis of the interferon responsive factor-1. The decrease in nuclear interferon responsive factor-1 and c-Rel results in alterations of the Ets-2-binding complex. Two transduction pathways, a cAMP-dependent and a cAMP-independent pathway, are involved in the inhibition of IL-12 gene expression and appear to differentially regulate the transcriptional factors involved. Because IL-12 participates in T cell activation and cytolytic T lymphocyte activity and promotes the differentiation of T helper cells into the Th1 subset, the understanding of the mechanisms that affect IL-12 production in normal and pathological conditions could contribute to immune response-based therapies or **vaccine** designs.

IT Major Concepts
Molecular Genetics (Biochemistry and Molecular Biophysics); Endocrine System (Chemical Coordination and Homeostasis)

IT Chemicals & Biochemicals
Ets protein: activation; **interleukin-12**;
interleukin-12 gene: transcription; nuclear factor kappa-B; pituitary adenylate cyclase-activating polypeptide; vasoactive intestinal peptide

RN 137061-48-4 (PITUITARY ADENYLATE CYCLASE-ACTIVATING POLYPEPTIDE)
37221-79-7 (VASOACTIVE INTESTINAL PEPTIDE)

L20 ANSWER 9 OF 24 BIOSIS COPYRIGHT 2001 BIOSIS

AN 1999:470750 BIOSIS

DN PREV199900470750

TI Pathology in schistosomiasis, mediated by a polarized TH2-type response, is prevented by a vaccination protocol employing RIL-12 as an **adjuvant** but protection is dependent on the induced expression of inducible **no synthase**.

AU Hesse, M. (1); Jankovic, D.; Cheever, A. W.; Modolell, M.; Wynn, T. A.

CS (1) Laboratory of Parasitic Diseases, National Institutes of Health,
Bethesda, MD USA

SO American Journal of Tropical Medicine and Hygiene, (Sept., 1999) Vol. 61,
No. 3 SUPPL., pp. 192-193.
Meeting Info.: 48th Annual Meeting of the American Society of Tropical
Medicine and Hygiene Washington, D.C., USA November 28-December 2, 1999
American Society of Tropical Medicine and Hygiene
. ISSN: 0002-9637.

DT Conference

LA English

IT Major Concepts
Clinical Immunology (Human Medicine, Medical Sciences); Infection;
Parasitology; Pharmacology

IT Diseases
schistosomiasis: parasitic disease

IT Chemicals & Biochemicals
inducible **NO synthase**: induced expression;
recombinant **IL-12**: **adjuvant**,
immunostimulant - drug

IT Alternate Indexing
Schistosomiasis (MeSH)

IT Methods & Equipment
vaccination protocol: immunization method

IT Miscellaneous Descriptors
polarized TH2-type response; **vaccine** development; Meeting
Abstract

ORGN Super Taxa
Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia;

Trematoda:
Platyhelminthes, Helminthes, Invertebrata, Animalia

ORGN Organism Name
mouse (Muridae): iNOS-deficient; Schistosoma mansoni (Trematoda):
parasite

ORGN Organism Superterms
Animals; Chordates; Helminths; Invertebrates; Mammals; Nonhuman
Mammals; Nonhuman Vertebrates; Platyhelminths; Rodents; Vertebrates

RN **125978-95-2 (NO SYNTHASE)**

L20 ANSWER 10 OF 24 BIOSIS COPYRIGHT 2001 BIOSIS

AN 1999:456607 BIOSIS

DN PREV199900456607

TI Shedding of membrane-bound CD14 from lipopolysaccharide-stimulated
macrophages by vasoactive intestinal peptide and pituitary adenylate
cyclase activating polypeptide.

AU Delgado, Mario (1); Leceta, Javier; Abad, Catalina; Martinez, Carmen;
Ganea, Doina; Gomariz, Rosa P.

CS (1) Departamento de Biologia Celular, Facultad de Biologia, Universidad
Complutense, 28040, Madrid Spain

SO Journal of Neuroimmunology, (Sept. 1, 1999) Vol. 99, No. 1, pp. 61-71.
ISSN: 0165-5728.

DT Article

LA English

SL English

AB Macrophage activation and deactivation play essential roles in the
initiation and maintenance of a successful immune response. Vasoactive
intestinal peptide (VIP) and pituitary adenylate cyclase activating
polypeptide (PACAP), two structurally related neuropeptides, act as

macrophage deactivating factors. We reported previously that VIP and PACAP inhibit IL-6, IL-12, TNFalpha and NO production, and enhance IL-10 production, from lipopolysaccharide (LPS)-stimulated macrophages. In this study, we demonstrate that VIP and PACAP down-regulate the expression of CD14, the membrane-bound LPS receptor, by inducing its rapid shedding.

The soluble CD14 released by VIP and PACAP corresponds in size to the soluble CD14 released by PMA. Neither VIP/PACAP nor PMA, affect the steady-state levels of CD14 mRNA. The CD14 shedding induced by VIP/PACAP is mediated through the PAC1 specific receptors and the major transduction pathway involves the protein kinase C (PKC). The VIP/PACAP inhibition of TNFalpha and NO occurs through both CD14-dependent and -independent mechanisms, whereas the inhibition of IL-6 production appears to be strictly CD14-dependent. The shedding of CD14 by VIP and PACAP represents an important mechanism by which these neuropeptides limit the macrophage inflammatory response.

IT Major Concepts
Biochemistry and Molecular Biophysics; Immune System (Chemical Coordination and Homeostasis)

IT Parts, Structures, & Systems of Organisms
macrophage: activation, blood and lymphatics, deactivation, lipopolysaccharide-stimulated, immune system

IT Chemicals & Biochemicals
lipopolysaccharide; phorbol 12-myristate 13-acetate; pituitary adenylate cyclase activating polypeptide: macrophage deactivating factor; protein kinase C; vasoactive intestinal peptide: macrophage deactivating factor; CD14 mRNA [CD14 messenger RNA]; CD14: membrane-bound, shedding; IL-10 [interleukin-10]: production; IL-12 [interleukin-12]; IL-6 [interleukin-6]; NO [nitric oxide]: production; TNF alpha [tumor necrosis factor alpha]

IT Miscellaneous Descriptors
immune response; neuroimmunomodulation

ORGN Super Taxa
Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia

ORGN Organism Name
mouse (Muridae): BALB/C

ORGN Organism Superterms
Animals; Chordates; Mammals; Nonhuman Mammals; Nonhuman Vertebrates; Rodents; Vertebrates

RN 10102-43-9 (NITRIC OXIDE)
16561-29-8 (PHORBOL 12-MYRISTATE 13-ACETATE)
137061-48-4 (PITUITARY ADENYLATE CYCLASE ACTIVATING POLYPEPTIDE)
141436-78-4 (PROTEIN KINASE C)
37221-79-7 (VASOACTIVE INTESTINAL PEPTIDE)

L20 ANSWER 11 OF 24 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1999:451219 BIOSIS
DN PREV199900451219
TI Synergistic effect of interferon-gamma and mannosylated liposome-incorporated doxorubicin in the therapy of experimental visceral leishmaniasis.
AU Kole, Labanyamoy; Das, Lopamudra; Das, Pijush K. (1)
CS (1) Indian Institute of Chemical Biology, 4 Raja S. C. Mullick Road, Calcutta, 700 032 India
SO Journal of Infectious Diseases, (Sept., 1999) Vol. 180, No. 3, pp.

811-820.
ISSN: 0022-1899.

DT Article
LA English
SL English

AB Active targeting of doxorubicin to macrophages was studied by incorporating it in mannosecoated liposomes by use of visceral leishmaniasis in BALB/c mice as the model macrophage disease.

Mannosylated
liposomal doxorubicin was more effective than liposomal doxorubicin or free doxorubicin. Because leishmaniasis is accompanied by **immunosuppression, immuno-stimulation** by interferon (IFN)-gamma was evaluated to act synergistically with mannosylated liposomal doxorubicin therapy. Combination chemotherapy with a suboptimal dose of IFN-gamma resulted in possibly complete elimination of spleen parasite burden. Analysis of mRNA levels of infected spleen cells suggested that targeted drug treatment together with IFN-gamma, in addition to greatly reducing parasite numbers, resulted in reduced levels of interleukin (IL)-4 but increased levels of IL-12 and inducible **nitric oxide** synthase. Such combination chemotherapy may provide a promising alternative for the cure of leishmaniasis, with a plausible conversion of antiparasitic T cell response from a Th2 to Th1 pattern indicative of long-term resistance.

IT Major Concepts
Immune System (Chemical Coordination and Homeostasis); Parasitology; Pharmacology

IT Parts, Structures, & Systems of Organisms
macrophage: blood and lymphatics, immune system; T cell: blood and lymphatics, immune system

IT Diseases
visceral leishmaniasis: experimental, model macrophage disease, parasitic disease

IT Chemicals & Biochemicals
doxorubicin: antiparasitic - drug, mannosylated
liposome-incorporation;
inducible **nitric oxide** synthase; interferon-gamma:
immunosuppressant - drug; **interleukin-12**;
interleukin-4; mannosylated liposome; mRNA [messenger RNA]

IT Alternate Indexing
Leishmaniasis, Visceral (MeSH)

ORGN Super Taxa
Flagellata: Protozoa, Invertebrata, Animalia; Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia

ORGN Organism Name
mouse (Muridae): BALB/c; Leishmania donovani (Flagellata): parasite

ORGN Organism Superterms
Animals; Chordates; Invertebrates; Mammals; Microorganisms; Nonhuman Mammals; Nonhuman Vertebrates; Protozoans; Rodents; Vertebrates

RN 23214-92-8 (DOXORUBICIN)
125978-95-2 (NITRIC OXIDE SYNTHASE)

L20 ANSWER 12 OF 24 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1999:445141 BIOSIS
DN PREV199900445141
TI Polarization of the immune response to the single immunodominant epitope of p38, a major Schistosoma mansoni egg antigen, generates Th1- or Th2-type cytokines and granulomas.

AU Chen, Yiguang; Boros, Dov L. (1)
 CS (1) Department of Immunology and Microbiology, WSU School of Medicine,
 540 E. Canfield Ave., Detroit, MI, 48201 USA
 SO Infection and Immunity, (Sept., 1999) Vol. 67, No. 9, pp. 4570-4577.
 ISSN: 0019-9567.
 DT Article
 LA English
 SL English
 AB In schistosomiasis mansoni, helminth eggs secrete soluble egg antigens
 (SEA) that induce T-cell-mediated granulomatous tissue responses. The
 cloned 38-kDa peptide (p38) of SEA was shown to induce and elicit
 Th1-type
 responsiveness in H-2k mice. Subsequently, the immunodominant T-cell
 epitope (P4) of p38 was shown to elicit pulmonary granuloma formation and
 Th1-type cytokine production in sensitized or infected mice. Here, we
 report that the immune response to p38 or P4 can be polarized to a Th1 or
 Th2 profile when the peptides are presented intraperitoneally in soluble
 recombinant interleukin-12 (IL-12) or alum **adjuvant**,
 respectively. The Th1 or Th2 profile was verified by cytokine secretion,
 enzyme-linked spot assay, and antibody isotype characterization.
 Importantly, the polarized immune response generated two types of
 pulmonary granulomas around injected P4-coated beads. The type 1
 granulomas were smaller and contained mononuclear cells and occasional
 thin strands of deposited collagen. In contrast, the type 2 lesions were
 larger and contained mononuclear cells, large numbers of eosinophils, and
 several thick bands of deposited collagen. By reverse transcription-PCR
 cytokine, message in the type 1 granuloma-bearing lungs was found for
 gamma interferon, tumor necrosis factor alpha, and inducible
nitric oxide synthase but not for IL-4 or IL-5.
 Conversely, lungs with type 2 granulomas had message only for IL-4 and
 IL-5. These results show that in the proper cytokine environment, the
 response to a strong Th1 inducer peptide can be deviated to a Th2
 profile.
 IT Major Concepts
 Biochemistry and Molecular Biophysics; Immune System (Chemical
 Coordination and Homeostasis); Parasitology
 IT Parts, Structures, & Systems of Organisms
 T cell: blood and lymphatics, immune system
 IT Diseases
 pulmonary granuloma: formation, respiratory system disease
 IT Chemicals & Biochemicals
 gamma interferon; inducible **nitric oxide** synthase;
 interleukin-4; interleukin-5; p38: immune response, immunodominant
 epitope, polarization, major Schistosoma mansoni egg antigen; soluble
 egg antigen: secretion; soluble recombinant **interleukin-**
12; tumor necrosis factor alpha
 ORGN Super Taxa
 Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia;
 Trematoda:
 Platyhelminthes, Helminthes, Invertebrata, Animalia
 ORGN Organism Name
 mouse (Muridae); Schistosoma mansoni (Trematoda): parasite
 ORGN Organism Superterms
 Animals; Chordates; Helminths; Invertebrates; Mammals; Nonhuman
 Mammals; Nonhuman Vertebrates; Platyhelminths; Rodents; Vertebrates
 RN 125978-95-2 (NITRIC OXIDE SYNTHASE)

L20 ANSWER 13 OF 24 BIOSIS COPYRIGHT 2001 BIOSIS
 AN 1999:136233 BIOSIS
 DN PREV199900136233
 TI Ex vivo effects of lactobacilli, streptococci, and bifidobacteria ingestion on cytokine and **nitric oxide** production in a murine model.
 AU Tejada-Simon, Maria Victoria; Ustunol, Zeynep; Pestka, James J. (1)
 CS (1) Dep. Food Sci. and Human Nutrition, Michigan State Univ., East Lansing, MI 48824-1224 USA
 SO Journal of Food Protection, (Feb., 1999) Vol. 62, No. 2, pp. 162-169. ISSN: 0362-028X.
 DT Article
 LA English
 AB Increasing numbers of functional foods and pharmaceutical preparations are being promoted with health claims based on the potential probiotic characteristics of lactic acid bacteria and on their capacity for **stimulating** the host **immune** system. However, the specific immune effects of oral administration of these microbes still remains undefined. In this study, we tested the hypothesis that production of immunologic mediators by leukocytes in mice is affected by orally administered lactic acid bacteria. The specific objectives of this study were to evaluate the effects of exposure to eight different lactic acid bacteria in mice on ex vivo cytokine and **nitric oxide** production in leukocyte cultures. Mice were gavaged with 1 X 10⁹ viable bacteria and peritoneal, Peyer's patch and splenic leukocytes were isolated 8 h later. These were cultured for 2 or 5 days in the presence or absence of mitogens and then interleukin (IL)-6, IL-12, interferon (IFN)-gamma, tumor necrosis factor (TNF)-alpha, and **nitric oxide** production was measured. The results revealed that Lactobacillus acidophilus and L. casei potentiated IL-6 and IL-12 production by peritoneal cells whereas L. acidophilus upregulated IFN-gamma and **nitric oxide**. In contrast, L. helveticus, L. gasseri, L. reuteri, and Bifidobacterium attenuated the production of IL-6, IFN-gamma, and **nitric oxide** by peritoneal cells. TNF-alpha was not detectable in peritoneal cultures. None of the bacteria altered ex vivo production of cytokines or **nitric oxide** by Peyer's patch or spleen cell cultures. Taken together, the results suggest that prior oral exposure to lactic acid bacteria could differentially potentiate or attenuate subsequent cytokine and **nitric oxide** production by peritoneal cells.

IT Major Concepts
 Foods; Immune System (Chemical Coordination and Homeostasis)
 IT Parts, Structures, & Systems of Organisms
 peritoneal leukocytes: blood and lymphatics, immune system; splenic leukocytes: blood and lymphatics, immune system; Peyer's patch leukocytes: blood and lymphatics, immune system
 IT Chemicals & Biochemicals
 interferon-gamma: production; **interleukin-12**: production; interleukin-6: production; **nitric oxide**: production; tumor necrosis factor-alpha: production
 IT Miscellaneous Descriptors
 functional foods: health food

ORGN Super Taxa

Gram-Positive Cocci: Eubacteria, Bacteria, Microorganisms; Irregular
Nonsporing Gram-Positive Rods: Actinomycetes and Related Organisms,
Eubacteria, Bacteria, Microorganisms; Muridae: Rodentia, Mammalia,
Vertebrata, Chordata, Animalia; Regular Nonsporing Gram-Positive Rods:
Eubacteria, Bacteria, Microorganisms

ORGN Organism Name

mouse (Muridae): animal model; Bifidobacterium (Irregular Nonsporing
Gram-Positive Rods): oral ingestion, probiotic; Lactobacillus
acidophilus (Regular Nonsporing Gram-Positive Rods): oral ingestion,
probiotic; Lactobacillus bulgaricus (Regular Nonsporing Gram-Positive
Rods): oral ingestion, probiotic; Lactobacillus casei (Regular
Nonsporing Gram-Positive Rods): oral ingestion, probiotic;
Lactobacillus gasseri (Regular Nonsporing Gram-Positive Rods): oral
ingestion, probiotic; Lactobacillus helveticus (Regular Nonsporing
Gram-Positive Rods): oral ingestion, probiotic; Lactobacillus reuteri
(Regular Nonsporing Gram-Positive Rods): oral ingestion, probiotic;
Streptococcus thermophilus (Gram-Positive Cocci): oral ingestion,
probiotic

ORGN Organism Superterms

Animals; Bacteria; Chordates; Eubacteria; Mammals; Microorganisms;
Nonhuman Mammals; Nonhuman Vertebrates; Rodents; Vertebrates

RN 10102-43-9 (NITRIC OXIDE)

L20 ANSWER 14 OF 24 BIOSIS COPYRIGHT 2001 BIOSIS

AN 1999:13829 BIOSIS

DN PREV199900013829

TI Immune suppression by recombinant interleukin (rIL)-12 involves
interferon

gamma induction of **nitric oxide** synthase 2 (iNOS)
activity: Inhibitors of NO generation reveal the extent of rIL-12
vaccine adjuvant effect.

AU Koblish, Holly Kurzawa; Hunter, Christopher A.; Wysocka, Maria;
Trinchieri, Giorgio; Lee, William M. F. (1)

CS (1) 663 Clin. Res. Build., 415 Curie Blvd., Univ. Pennsylvania,
Philadelphia, PA 19104-6140 USA

SO Journal of Experimental Medicine, (Nov. 2, 1998) Vol. 188, No. 9, pp.
1603-1610.

ISSN: 0022-1007.

DT Article

LA English

AB Recombinant interleukin 12 (IL-12) can profoundly suppress cellular
immune

responses in mice. To define the underlying mechanism, recombinant murine
(rm)IL-12 was given to C57BL/6 mice undergoing alloimmunization and found
to transiently but profoundly suppress in vivo and in vitro allogeneic
responses and in vitro splenocyte mitogenic responses. Use of

neutralizing

antibodies and genetically deficient mice showed that IFN-gamma (but not
TNF-alpha) mediated rmIL-12-induced immune suppression. Splenocyte
fractionation studies revealed that adherent cells from rmIL-12-treated
mice suppressed the mitogenic response of normal nonadherent cells to
concanavalin A and IL-2. Addition of an inhibitor of **nitric
oxide** synthase (NOS) restored mitogenic responses, and inducible
(i)NOS-/- mice were not immunosuppressed by rmIL-12. These results support
the view that suppression of T cell responses is due to NO produced by
macrophages responding to the high levels of IFN-gamma induced by
rmIL-12.

✓ 9/98
11/98

When a NOS inhibitor was given with rmIL-12 during vaccination of A/J mice with irradiated SCK tumor cells, immunosuppression was averted and the extent of rmIL-12's ability to enhance induction of protective antitumor immunity was revealed. This demonstrates that rmIL-12 is an effective **vaccine adjuvant** whose efficacy may be masked by its transient immunosuppressive effect.

IT Major Concepts
Immune System (Chemical Coordination and Homeostasis); Pharmacology

IT Chemicals & Biochemicals
interferon gamma; **nitric oxide** synthase 2: activity, induction; **nitric oxide**: synthesis; recombinant **interleukin-12**: immunosuppressive agent, **vaccine**

RN 125978-95-2 (NITRIC OXIDE SYNTHASE)
10102-43-9 (NITRIC OXIDE)

L20 ANSWER 15 OF 24 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1998:389812 BIOSIS
DN PREV199800389812
TI Effects of interleukin-12 in vitro on pancreatic islets isolated from normal rodents and from non-obese diabetic mice.
AU Sternesjo, J. (1); Sandler, S.
CS (1) Dep. Med. Cell Biol., Uppsala Univ. Biomedicum, P.O. Box 571, S-751 23 Uppsala Sweden
SO Journal of Endocrinology, (July, 1998) Vol. 158, No. 1, pp. 69-75. ISSN: 0022-0795.
DT Article
LA English
AB Administration of the T-helper 1 (Th1) cell promoting cytokine interleukin-12 (IL-12) accelerates the development of autoimmune diabetes in non-obese diabetic (NOD) mice. In this study we examined the effects of IL-12 on isolated islets from NMRI (Naval Medical Research Institute-established) mice, Sprague-Dawley (S-D) rats and NOD mice. NMRI and S-D islets were cultured in medium RPMI 1640 + 10% fetal calf serum and exposed for 48 h to recombinant mouse IL-12 (0, 0.1, 1 and 10 ng/ml). Islet glucose metabolism, as measured by glucose oxidation rate, was suppressed by about 25% in NMRI islets exposed to 10 ng/ml IL-12. In rat islets 0.1 ng/ml IL-12 induced a 20% decrease in glucose oxidation rate. Islets cultured with 10 ng/ml IL-12 showed a decrease in medium insulin accumulation both in mouse and rat. Glucose-stimulated insulin release was lowered in rat islets exposed to 10 ng/ml IL-12, but not affected in NMRI islets. In NMRI islets IL-12 did not influence **nitric oxide** production as measured by nitrite formation. In rat islets IL-12 induced a decrease in nitrite formation compared with control islets. Islets were isolated from female NOD mice (age 5, 12, 20 and 26 weeks) and examined either immediately or cultured for 7 days with 10 ng/ml IL-12 alone or in combination with 4 ng/ml of the T-cell stimulating cytokine interleukin-2 (IL-2). In the age groups >5 weeks of age the glucose-stimulated insulin release was lower in freshly isolated compared with cultured control islets. IL-2+IL-12 addition induced a small decrease

in glucose-stimulated insulin release in islets from 12-week-old animals. With increasing age the DNA content in freshly isolated islets increased due to immune cell infiltration. The DNA content in cultured islets was decreased by 40-60% compared with freshly isolated islets in the age groups over 5 weeks. Islet insulin content was similar in both freshly isolated and cultured islets. None of the cytokines, either alone or in combination, affected islet DNA or insulin content. We conclude that

IL-12

has minor suppressive effects in vitro on normal rodent islets. It is likely that the reported accelerated diabetes development of IL-12 administration to NOD mice in vivo is not mediated by a direct toxic effect to the islets. The suppressed insulin release in NOD mouse islets treated with IL-2+IL-12 suggests, however, that the accelerating effect might partly be attributed to **stimulation of immune** cells present in the insulinitic lesion.

IT Major Concepts

Endocrine System (Chemical Coordination and Homeostasis); Immune System

(Chemical Coordination and Homeostasis)

IT Parts, Structures, & Systems of Organisms

pancreatic islets: endocrine system; T-helper lymphocyte: immune system

IT Diseases

diabetes: accelerated, endocrine disease/pancreas, metabolic disease

IT Chemicals & Biochemicals

insulin: release; **interleukin-12**; interleukin-2;

nitric oxide; DNA

ORGN Super Taxa

Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia; Rodentia: Mammalia, Vertebrata, Chordata, Animalia

ORGN Organism Name

mouse (Muridae): NMRI, NOD; rat (Muridae): Sprague-Dawley; rodent (Rodentia)

ORGN Organism Superterms

Animals; Chordates; Mammals; Nonhuman Mammals; Nonhuman Vertebrates; Rodents; Vertebrates

RN 9004-10-8 (INSULIN)

10102-43-9 (NITRIC OXIDE)

L20 ANSWER 16 OF 24 BIOSIS COPYRIGHT 2001 BIOSIS

AN 1998:216334 BIOSIS

DN PREV199800216334

TI The role of Il-12 in experimental Trypanosoma cruzi infection.

AU Silva, J. S. (1); Aliberti, J. C. S.; Martins, G. A.; Souza, M. A.; Souto,

J. T.; Padua, M. A.

CS (1) Departamento de Parasitologia, Microbiologia e Imunologia, FMRP, USP, Av. Bandeirantes 3900, 14049-9000 Ribeirao Preto, SP Brazil

SO Brazilian Journal of Medical and Biological Research, (Jan., 1998) Vol. 31, No. 1, pp. 111-115.

ISSN: 0100-879X.

DT Article

LA English

AB Host resistance to Trypanosoma cruzi infection is dependent on both natural and acquired immune responses. During the early acute phase of infection in mice, natural killer (NK) cell-derived IFN-gamma is involved in controlling intracellular parasite replication, mainly through the

induction of **nitric oxide** biosynthesis by activated macrophages. We have shown that IL-12, a powerful inducer of IFN-gamma production by NK cells, is synthesized soon after trypomastigote-macrophage interaction. The role of IL-12 in the control of *T. cruzi* infection in vivo was determined by treating infected mice with anti-IL-12 monoclonal antibody (mAb) and analyzing both parasitemia and mortality during the acute phase of infection. The anti-IL-12 mAb-treated mice had higher levels of parasitemia and mortality compared to control mice.

Also,

treatment of infected mice with mAb specific for IFN-gamma or TNF-alpha inhibited the protective effect of exogenous IL-12. On the other hand, TGF-B and IL-10 produced by infected macrophages inhibited the induction and effects of IL-12. Therefore, while IL-12, TNF-alpha and IFN-gamma correlate with resistance to *T. cruzi* infection, TGF-B and IL-10 promote susceptibility. These results provide support for a role of innate immunity in the control of *T. cruzi* infection. In addition to its protective role, IL-12 may also be involved in the modulation of *T. cruzi*-induced myocarditis, since treatment of infected mice with IL-12 or anti-IL-12 mAb leads to an enhanced or decreased inflammatory infiltrate in the heart, respectively. Understanding the role of the cytokines produced during the acute phase of *T. cruzi* infection and their involvement in protection and pathogenesis would be essential to devise new **vaccines** or therapies.

IT Major Concepts

Immune System (Chemical Coordination and Homeostasis); Parasitology

IT Parts, Structures, & Systems of Organisms

macrophage: blood and lymphatics, immune system; natural killer cell: blood and lymphatics, immune system

IT Diseases

Trypanosoma cruzi infection: parasitic disease

IT Chemicals & Biochemicals

cytokines; **Il-12 [interleukin-12]**: cytokine

IT Miscellaneous Descriptors

experimental infections; pathogenesis

ORGN Super Taxa

Flagellata: Protozoa, Invertebrata, Animalia; Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia

ORGN Organism Name

mouse (Muridae); Trypanosoma-cruzi (Flagellata): parasite

ORGN Organism Superterms

Animals; Chordates; Invertebrates; Mammals; Microorganisms; Nonhuman Mammals; Nonhuman Vertebrates; Protozoans; Rodents; Vertebrates

L20 ANSWER 17 OF 24 BIOSIS COPYRIGHT 2001 BIOSIS

AN 1998:170056 BIOSIS

DN PREV199800170056

TI Control of coccidiosis: Lessons from other sporozoa.

AU Cox, F. E. G. (1)

CS (1) Div. Life Sci., Kings Coll. London, Campden Hill Road, London W8 7AH UK

SO International Journal for Parasitology, (Jan., 1998) Vol. 28, No. 1, pp. 165-179.

ISSN: 0020-7519.

DT General Review

LA English

AB Coccidiosis is the most important parasitic infection in poultry worldwide

and also causes problems in cattle, sheep and goats. Control is largely limited to good husbandry and prophylactic chemotherapy using a range of drugs against which resistance is rapidly acquired. Attempts at vaccination using conventional **vaccines** have been disappointing and there is now a need for a new approach. Research into the immunology of coccidiosis has lagged behind that of other sporozoans and there are useful lessons that might be learned from studies on toxoplasmosis, cryptosporidiosis, theileriosis and malaria. In these infections the emphasis has turned to the cytokine network that drives the response towards protection. Central to these studies are the roles of interferon-gamma, interleukin-12 and activated macrophages with the involvement of **nitric oxide** in parasite killing.

Cytotoxic T cells have also increasingly been implicated. Research has shown that different immune responses can be elicited by manipulating the

cytokine system and these new concepts can be applied to the design of peptide or recombinant **vaccines**, and the possibilities of developing such **vaccines** against coccidiosis will be discussed.

IT Major Concepts

Parasitology

IT Parts, Structures, & Systems of Organisms

activated macrophages: blood and lymphatics, immune system; cytotoxic

T

cells: blood and lymphatics, immune system

IT Diseases

coccidiosis: parasitic disease; cryptosporidiosis: digestive system disease, parasitic disease; theileriosis: parasitic disease; toxoplasmosis: parasitic disease

IT Chemicals & Biochemicals

interferon-gamma; **interleukin-12**

IT Methods & Equipment

vaccination: prophylactic method

IT Miscellaneous Descriptors

disease control strategies; immunology; prophylactic chemotherapy

L20 ANSWER 18 OF 24 BIOSIS COPYRIGHT 2001 BIOSIS

AN 1998:125261 BIOSIS

DN PREV199800125261

TI The debate over the effector function of eosinophils in helminth infection: New evidence from studies on the regulation of **vaccine** immunity by IL-12.

AU Wynn, Thomas A. (1)

CS (1) Immunobiol. Section, Lab. Parasitic Diseases, Natl. Inst. Allergy Infectious Diseases, Natl. Institutes Health, Bethesda, MD 20892 USA

SO Memorias do Instituto Oswaldo Cruz, (Dec. 30, 1997 (1998)) Vol. 92, No. SUPPL. 2, pp. 105-108. ISSN: 0074-0276.

DT Article

LA English

AB The production of Th1-type cytokines is associated with strong cell-mediated immunity while Th2-type cytokines are typically involved in the generation of humoral immune responses. In mice vaccinated a single time (1X) with attenuated cercariae of *Schistosoma mansoni*, the immunity induced is highly dependent on CD4+ T cells and IFN-gamma. In contrast, mice vaccinated multiple times (3X) have decreased IFN-gamma expression,

develop a more dominant Th2-type cytokine response as well as protective antibodies which can passively transfer immunity to naive recipients. Previously, we demonstrated the ability of IL-12, a potent IFN-gamma-inducing cytokine to enhance (IX) schistosome cell-mediated immunity when administered during the period of immunization. More recently, we asked what effects IL-12 would have on the development humoral-based immunity. While multiply-immunized/saline-treated mice demonstrated a 70-80% reduction in parasite burden, 3X/IL-12-vaccinated animals displayed an even more striking >90% reduction in challenge infection, with many mice in the later group demonstrating complete protection. Analysis of pulmonary cytokine mRNA responses demonstrated that control challenged mice elicited a dominant Th2-type response, 3X/saline-vaccinated produced a mixed Th1/Th2-type cytokine response, while 3X/IL-12-immunized animals displayed a dominant Th1-type response. The IL-12-treated group also showed a marked reduction in total serum IgE and tissue eosinophilia while SWAP-specific IgG2a and IgG2b Abs were elevated. Interestingly, animals vaccinated with IL-12 also showed a highly significant increase in total Ig titers specific for IrV-5, a known protective antigen. More importantly, 3X/IL-12 serum alone, when transferred to naive mice reduced worm burdens by over 60% while 3X/saline serum transferred significantly less protection. Nevertheless, animals vaccinated in the presence of IL-12 also develop macrophages with enhanced nitric oxide dependent killing activity against the parasites. Together these observations suggest that IL-12, initially described as an **adjuvant** for cell-mediated immunity, may also be used as an **adjuvant** for promoting both humoral and cell-mediated protective responses.

IT Major Concepts
Immune System (Chemical Coordination and Homeostasis); Parasitology

IT Parts, Structures, & Systems of Organisms
eosinophil: blood and lymphatics, immune system; CD4 positive T cell: immune system

IT Chemicals & Biochemicals
immunoglobulin E; immunoglobulin G2a; immunoglobulin G2b; interferon-gamma; **interleukin-12**

IT Miscellaneous Descriptors
humoral immune response; **vaccine** immunity

ORGN Super Taxa
Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia;

Trematoda:
Platyhelminthes, Helminthes, Invertebrata, Animalia

ORGN Organism Name
mouse (Muridae): parasite host; Schistosoma-mansoni (Trematoda): parasite

ORGN Organism Superterms
Animals; Chordates; Helminths; Invertebrates; Mammals; Nonhuman Mammals; Nonhuman Vertebrates; Platyhelminths; Rodents; Vertebrates

L20 ANSWER 19 OF 24 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1998:6581 BIOSIS
DN PREV199800006581
TI Cytokines and **nitric oxide** as effector molecules against parasitic infections.
AU Liew, Foo Y. (1); Wei, Xiao-Qing; Proudfoot, Lorna

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L2 1809 S NITRIC OXIDE
L3 85 S NO SYNTHASE
L4 5 S L1 AND (L2 OR L3)
L5 21 S L NAME OR L NMMA
L6 66 S ?METHYL ARGININE OR ?ARGININE (W) (METHYLESTER OR METHYL
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L8 1 S L1 AND L7
L9 5 S L8 OR L4

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AN 2001-007219 [01] WPIDS
DNC C2001-001834
TI Protecting pancreatic islet beta-cells from immune system-mediated
toxicity, used to prevent Type I diabetes, by transducing beta-cells with
genetically modified adeno-associated virus vectors.
DC B04 D16
IN BLEICH, D; NADLER, J L; PRASAD, K
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RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL
OA PT SD SE SL SZ TZ UG ZW

CS (1) Dep. Immunol., Univ. Glasgow, Glasgow G11 6NT UK
 SO Philosophical Transactions of the Royal Society of London B Biological Sciences, (Sept. 29, 1997) Vol. 352, No. 1359, pp. 1311-1315. ✓
 ISSN: 0962-8436.
 DT Article
 LA English
 AB **Nitric oxide** (NO) derived from L-arginine by the catalytic action of inducible **NO synthase** (iNOS) plays an important role in killing parasites. Many cell types express high levels of iNOS when activated by a number of **immunological stimuli** which include interferon-gamma (IFN-gamma), tumour necrosis factor alpha, and lipopolysaccharide. IFN-gamma is typically produced by the Th1 subset of CD4+ T cells, whose differentiation depends on interleukin-12 (IL-12) produced by macrophages. Mice with a disrupted iNOS gene were highly susceptible to Leishmania major infection compared with similarly infected control wild-type mice. The mutant mice developed significantly higher levels of TH1-cell response compared with the control mice, suggesting that NO is likely to be the effector molecule in the immunological control of this and other intracellular parasitic infections. To ensure their survival, the Leishmania parasites have evolved effective means to inhibit NO synthesis. The highly conserved major surface glycolipids, glycoinositol-phospholipids and lipophosphoglycan (LPG), of Leishmania are potent inhibitors of NO synthesis. Furthermore, LPG can also inhibit IL-12 synthesis, thereby indirectly blocking the induction of iNOS. The evolutionary and therapeutic implications of these findings are discussed.

IT Major Concepts
 Immune System (Chemical Coordination and Homeostasis); Parasitology

IT Chemicals & Biochemicals
 cytokines; glycoinositol-phospholipids; interferon-gamma; **interleukin-12** [IL-12]; iNOS gene [inducible **nitric oxide** synthase gene]; lipophosphoglycan; **nitric oxide**; surface glycolipids; tumor necrosis factor-alpha

ORGN Super Taxa
 Flagellata: Protozoa, Invertebrata, Animalia; Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia

ORGN Organism Name
 mouse (Muridae): parasite host; Leishmania (Flagellata): parasite; Leishmania-major (Flagellata): parasite

ORGN Organism Superterms
 Animals; Chordates; Invertebrates; Mammals; Microorganisms; Nonhuman Mammals; Nonhuman Vertebrates; Protozoans; Rodents; Vertebrates

RN **10102-43-9 (NITRIC OXIDE)**
125978-95-2 (NITRIC OXIDE SYNTHASE)

L20 ANSWER 20 OF 24 BIOSIS COPYRIGHT 2001 BIOSIS
 AN 1997:392518 BIOSIS
 DN PREV199799691721
 TI Lipopolysaccharide and monophosphoryl lipid A differentially regulate interleukin-12, gamma interferon, and interleukin-10 mRNA production in murine macrophages.
 AU Salkowski, Cindy A.; Detore, Gregory R.; Vogel, Stefanie N. (1)
 CS (1) Dep. Microbiol. Immunol., Uniformed Services Univ. Health Sci., 4301 Jones Bridge Rd., Bethesda, MD 20814 USA
 SO Infection and Immunity, (1997) Vol. 65, No. 8, pp. 3239-3247.

ISSN: 0019-9567.

DT Article

LA English

AB Monophosphoryl lipid A (MPL) is a nontoxic derivative of the lipid A region of lipopolysaccharide (LPS) that is being developed as both an **adjuvant** and prophylactic drug for septic shock. We compared the ability of LPS and MPL to induce interleukin-10 (IL-10), IL-12 p35, IL-12 p40, gamma interferon (IFN-gamma), glucocorticoid receptor (GR), IL-1 receptor antagonist (IL-1ra), and inducible **nitric oxide** synthase mRNA expression in murine peritoneal macrophages. These genes were chosen for their ability to positively or negatively regulate the host immune response and thus for their potential involvement in MPL-induced adjuvant activity or in its ability to protect against sepsis.

LPS was a more potent inducer of IL-12 p35, IL-12 p40, and IFN-gamma mRNA, as well as of IL-12 protein, than MPL. In contrast, MPL induced higher levels of IL-10 mRNA than did LPS from 1 to 1,000 ng/ml. In general, MPL was not a more potent inducer of negative regulatory genes, since MPL and LPS induced similar levels of GR and IL-1ra mRNA. Addition of anti-IL-10 antibody to cultures increased the induction of MPL-induced IL-12 p35, IL-12 p40, and IFN-gamma mRNA, suggesting that the enhanced production of IL-10 by MPL-stimulated macrophages contributes to decreased production of mRNA for IL-12 (p35 and p40) and IFN-gamma. Conversely, the addition of exogenous IL-10 to LPS-treated macrophages reduced the mRNA expression of these cytokine genes. These studies suggest that enhanced production of IL-10 by MPL-stimulated macrophages may contribute to the reduced toxicity of MPL through its negative action on induction of cytokines shown to enhance endotoxicity.

IT Major Concepts
Biochemistry and Molecular Biophysics; Blood and Lymphatics (Transport and Circulation); Cell Biology; Endocrine System (Chemical Coordination and Homeostasis); Enzymology (Biochemistry and Molecular Biophysics); Immune System (Chemical Coordination and Homeostasis); Infection; Membranes (Cell Biology); Toxicology

IT Chemicals & Biochemicals
LIPID A; **NITRIC OXIDE SYNTHASE**

IT Miscellaneous Descriptors
BACTERIAL DISEASE; BLOOD AND LYMPHATICS; ENDOTOXICITY; GAMMA-INTERFERON; GLUCOCORTICOID RECEPTOR; HOST IMMUNE RESPONSE; IMMUNE SYSTEM; INDUCIBLE **NITRIC OXIDE SYNTHASE**; INTERLEUKIN-1 RECEPTOR ANTAGONIST; INTERLEUKIN-10; **INTERLEUKIN-12 P35**; **INTERLEUKIN-12 P40**; LIPOPOLYSACCHARIDE; MESSENGER RNA; MONOPHOSPHORYL LIPID A; MRNA; PERITONEAL MACROPHAGES; SEPTIC SHOCK

ORGN Super Taxa
Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia

ORGN Organism Name
mouse (Muridae)

ORGN Organism Superterms
animals; chordates; mammals; nonhuman mammals; nonhuman vertebrates; rodents; vertebrates

RN 95991-05-2 (LIPID A)

125978-95-2 (NITRIC OXIDE SYNTHASE)

L20 ANSWER 21 OF 24 BIOSIS COPYRIGHT 2001 BIOSIS

AN 1997:204629 BIOSIS

DN PREV199799503832

TI Interleukin-12 synthesis is a required step in trehalose dimycolate-induced activation of mouse peritoneal macrophages.

AU Oswald, Isabelle P.; Dozois, Charles M.; Petit, Jean-Francois; Lemaire, Genevieve (1)

CS (1) URA CNRS 1116, Batiment 430, Univ. Paris Sud, 91405 Orsay Cedex France

SO Infection and Immunity, (1997) Vol. 65, No. 4, pp. 1364-1369. ISSN: 0019-9567.

DT Article

LA English

AB Trehalose dimycolate (TDM), a glycolipid present in the cell wall of Mycobacterium spp., is a powerful **immunostimulant**. TDM primes murine macrophages (M-vphi) to produce **nitric oxide** (NO) and to develop antitumoral activity upon activation with low doses

of lipopolysaccharide (LPS). In this study, we investigated the ability of TDM to induce interleukin 12 (IL-12) and the role of this cytokine in TDM-induced activation of murine M-vphi. RNA isolated from peritoneal exudate cells (PEC) collected at different times after TDM injection was used to determine IL-12 (p35 and p40 subunits) and gamma interferon (IFN-gamma) mRNA levels by semiquantitative reverse transcriptase-PCR. Constitutive expression of IL-12p35 was observed in PEC from untreated as well as from TDM-injected mice. In contrast, expression of the IL-12p40 subunit was almost undetectable in control PEC but was dramatically upregulated in PEC from TDM-injected mice. IL-12p40 expression peaked at

8 h and subsided to baseline levels at 39 h postinjection. TDM was also able

to induce IFN-gamma expression; however, kinetics of induction of IFN-gamma was different from that of IL-12p40. Maximal levels of

IFN-gamma mRNA were reached by 24 h and did not return to baseline by 4 days. In addition, pretreatment of mice with neutralizing monoclonal antibodies directed against IL-12 (C15.6.7 and C15.1.2) blocked IFN-gamma mRNA induction in PEC from TDM-treated mice. We further determined if the induction of IL-12 and/or IFN-gamma contributes to the in vivo priming effect of TDM on peritoneal M-vphi. TDM-injected mice were treated in

vivo with anti-IL-12 or anti-IFN-gamma (XMG.1.6) monoclonal antibodies. TDM-primed M-vphi were then activated in vitro with LPS and tested for their ability to produce NO and to develop cytostatic activity toward cocultivated L1210 tumor cells. Priming of M-vphi by TDM was completely blocked by in vivo neutralization of either IL-12 or IFN-gamma as demonstrated by an absence of tumoricidal activity and NO production by TDM-elicited M-vphi in the presence of LPS. Taken together our results show that TDM, a defined molecule from M. tuberculosis, induces in vivo production of IL-12. Moreover, synthesis of IL-12 mediates TDM priming of mouse peritoneal M-vphi through IFN-gamma induction.

IT Major Concepts

Biochemistry and Molecular Biophysics; Blood and Lymphatics (Transport and Circulation); Cell Biology; Endocrine System (Chemical Coordination

and Homeostasis); Immune System (Chemical Coordination and Homeostasis); Metabolism

IT Chemicals & Biochemicals
TREHALOSE

IT Miscellaneous Descriptors
BLOOD AND LYMPHATICS; ENDOCRINE SYSTEM; IMMUNE SYSTEM;
INTERFERON-GAMMA; INTERLEUKIN-12; MACROPHAGE;
TREHALOSE

ORGN Super Taxa
Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia

ORGN Organism Name
mouse (Muridae)

ORGN Organism Superterms
animals; chordates; mammals; nonhuman mammals; nonhuman vertebrates;
rodents; vertebrates

RN 99-20-7 (TREHALOSE)

L20 ANSWER 22 OF 24 BIOSIS COPYRIGHT 2001 BIOSIS

AN 1997:24081 BIOSIS

DN PREV199799323284

TI Toxoplasma gondii: Evidence of interleukin-12-dependent and -independent pathways of interferon-gamma production induced by an attenuated parasite strain.

AU Scharton-Kersten, Tanya (1); Caspar, Patricia (1); Sher, Alan (1); Denkers, Eric Y.

CS (1) Immunobiol. Sect., Lab. Parasitic Dis., Natl. Inst. Allergy Infect. Dis., Bethesda, MD 20892 USA

SO Experimental Parasitology, (1996) Vol. 84, No. 2, pp. 102-114. ISSN: 0014-4894.

DT Article

LA English

AB Immunity in mice infected with Toxoplasma gondii is dependent upon the ability to generate protective levels of the cytokine IFN-gamma. In this report, we present evidence that the attenuated **vaccine** strain, ts-4, induces the latter cytokine by both IL-12-dependent and -independent pathways. In contrast, strain ME49 appears to induce IFN-gamma wholly in dependence upon IL-12. Thus, 88% of wild-type C57BL/6 mice treated with anti-IL-12 mAb survive ts-4 infection, unlike similarly treated ME49-infected animals. Moreover, while anti-IL-12 treatment reduced early IFN-gamma and **nitric oxide** production to background levels in ts-4-infected scid animals, the same treatment in infected C57BL/6 mice had no effect on production of the latter mediators. In addition, we found that anti-IL-12 treatment induces 100% mortality in CD4+-deficient MHC class II knockout mice infected with ts-4. Finally, production of **nitric oxide** (a molecule implicated in parasite control) was abrogated in ts-4-infected scid mice following depletion of IFN-gamma producing NK cells. Together, our results suggest that ts-4 induces IL-12-dependent and -independent IFN-gamma production in normal mice, but ME49 induces the latter cytokine only in dependence upon IL-12. Our data, furthermore, implicate involvement of T cells in the IL-12-independent component of the IFN-gamma response.

IT Major Concepts
Blood and Lymphatics (Transport and Circulation); Cell Biology;
Endocrine System (Chemical Coordination and Homeostasis); Genetics;
Immune System (Chemical Coordination and Homeostasis); Parasitology

IT Chemicals & Biochemicals
NITRIC OXIDE

IT Miscellaneous Descriptors
 BLOOD AND LYMPHATICS; C57BL/6 MOUSE; C57BL/6 SCID MOUSE; IMMUNE
 SYSTEM;
 INTERFERON-GAMMA; **INTERLEUKIN-12**; **NITRIC**
OXIDE; PARASITE; PARASITE HOST; PARASITOLOGY; PRODUCTION;
 SEVERE COMBINED IMMUNODEFICIENCY; STRAIN-ME49; STRAIN-TS-4; T CELL

ORGN Super Taxa
 Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia; Sporozoa:
 Invertebrata, Protozoa, Animalia

ORGN Organism Name
 Muridae (Muridae); Toxoplasma gondii (Sporozoa)

ORGN Organism Superterms
 animals; chordates; invertebrates; mammals; microorganisms; nonhuman
 mammals; nonhuman vertebrates; protozoans; rodents; vertebrates

RN 10102-43-9 (**NITRIC OXIDE**)

L20 ANSWER 23 OF 24 BIOSIS COPYRIGHT 2001 BIOSIS
 AN 1995:299361 BIOSIS
 DN PREV199598313661
 TI IL-12 enhances **vaccine**-induced immunity to *Schistosoma mansoni*
 in mice and decreases T helper 2 cytokine expression, IgE production and
 tissue eosinophilia.

AU Wynn, Thomas A. (1); Jankovic, Dragana; Hieny, Sara; Cheever, Allen W.;
 Sher, Alan

CS (1) 9000 Rockville Pike, Natl. Inst. Health, Build. 4/126, Bethesda, MD
 20892 USA

SO Journal of Immunology, (1995) Vol. 154, No. 9, pp. 4701-4709.
 ISSN: 0022-1767.

DT Article
 LA English

AB Vaccination of mice with radiation-attenuated cercariae of *Schistosoma*
mansoni results in a highly significant but partial protection against
 challenge infection. This immunity is dependent on CD4+ T cells, and
 because of its suppression by anti-IFN-gamma, appears to be caused by a
 Th1 response. Nevertheless, both Th1 and Th2 lymphokines are expressed in
 vaccinated and challenged mice, and we hypothesized that the expression
 of
 the latter group of down-regulatory cytokines may be responsible for the
 failure to obtain complete protection. Because IL-12 is a key cytokine
 that suppresses Th2-like responses, we asked whether IL-12 could increase
vaccine-induced immunity to *S. mansoni*. Indeed, administration of
 IL-12 significantly reduced worm burdens following a challenge infection.
 IL-12-treated animals displayed a marked increase in pulmonary IFN-gamma
 and IL-12 p40 mRNA expression, while levels of IL-4, IL-5, and IL-13 were
 suppressed significantly during the period of vaccination. A marked
 decrease in serum IgE and tissue eosinophilia, two responses regulated by
 Th2 cytokines, was also observed. Surprisingly, IL-12-treated/vaccinated
 mice failed to demonstrate a significant increase in IFN-gamma,
 TNF-alpha,
 or **nitric oxide** synthase mRNA at the time of challenge
 infection when compared with vaccinated controls, but did, however,
 display significantly suppressed Th2 cytokine mRNA production. Together,
 these data demonstrate that exogenous IL-12 regulates Th1/Th2 responses
 during immunization with irradiated cercariae, and suggest that this
 cytokine may be used to increase **vaccine**-induced immunity to *S.*

mansoni.

IT Major Concepts
 Biochemistry and Molecular Biophysics; Blood and Lymphatics (Transport and Circulation); Cell Biology; Endocrine System (Chemical Coordination and Homeostasis); Immune System (Chemical Coordination and Homeostasis); Membranes (Cell Biology); Parasitology; Pharmacology; Physiology

IT Miscellaneous Descriptors
 IMMUNOGLOBULIN E; INTERLEUKIN-12

ORGN Super Taxa
 Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia;

Trematoda:
 Platyhelminthes, Helminthes, Invertebrata, Animalia

ORGN Organism Name
 mouse (Muridae); Schistosoma mansoni (Trematoda)

ORGN Organism Superterms
 animals; chordates; helminths; invertebrates; mammals; nonhuman mammals; nonhuman vertebrates; platyhelminths; rodents; vertebrates

L20 ANSWER 24 OF 24 BIOSIS COPYRIGHT 2001 BIOSIS

AN 1995:35584 BIOSIS

DN PREV199598049884

TI Elevated expression of Th1 cytokines and **nitric oxide** synthase in the lungs of vaccinated mice after challenge infection with *Schistosoma mansoni*.

AU Wynn, Thomas A. (1); Oswald, Isabelle P.; Eltoum, Isam A.; Caspar, Patricia; Lowenstein, Charles J.; Lewis, Fred A.; James, Stephanie L.; Sher, Alan

CS (1) 9000 Rockville Pike, Natl. Inst. Health, Building 4, Room 126, Bethesda, MD 20892 USA

SO Journal of Immunology, (1994) Vol. 153, No. 11, pp. 5200-5209. ISSN: 0022-1767.

DT Article

LA English

AB C57BL/6 mice were vaccinated with irradiated cercariae of *Schistosoma mansoni*, and, at various times after challenge infection, total lung mRNA was isolated to assess the induction of several cytokines that previously had been shown in in vitro studies to be involved in the activation of macrophages and/or endothelial cells for **nitric oxide** (NO) production and killing of schistosomula. Vaccinated mice demonstrated a highly significant increase in IFN-gamma mRNA upon subsequent infection when compared with infected nonvaccinated controls. A similar, although less dramatic, increase in two other macrophage-activating cytokines, TNF-alpha and IL-2, also was observed. In contrast, although the Th2 cytokines IL-4, IL-5, IL-10, and IL-13 were elevated in challenged vaccinated animals, only IL-10 and IL-13 showed increases that were significant with respect to the mRNA levels observed in challenged controls. Neutralization of IFN-gamma reduced immunity in vaccinated animals and resulted in decreased IFN-gamma, IL-2, IL-10, TNF-alpha, and IL-12 p40 but markedly increased IL-4, IL-5, and IL-13 mRNA expression and serum IgE levels. Pulmonary **NO synthase** expression was elevated in immunized mice at a time at which immune elimination of schistosomula is believed to occur. Moreover, suppression of **NO synthase** activity with the inhibitor aminoguanidine reduced

immunity, as measured by a 32 to 33% increase in worm burden. Together, these data support previous in vitro studies that suggest a role for NO in schistosomulum killing. Furthermore, the observation that the down-regulatory cytokines IL-4, IL-10, and IL-13 are induced together with IFN-gamma may provide an explanation for the failure of this vaccine to provide complete protection.

IT Major Concepts
 Blood and Lymphatics (Transport and Circulation); Endocrine System (Chemical Coordination and Homeostasis); Enzymology (Biochemistry and Molecular Biophysics); Immune System (Chemical Coordination and Homeostasis); Parasitology; Respiratory System (Respiration)

IT Chemicals & Biochemicals
NITRIC OXIDE SYNTHASE

IT Miscellaneous Descriptors
 INTERFERON-GAMMA; INTERLEUKIN-10; **INTERLEUKIN-12**;
 INTERLEUKIN-13; INTERLEUKIN-2; INTERLEUKIN-4; INTERLEUKIN-5; TUMOR NECROSIS FACTOR-ALPHA

ORGN Super Taxa
 Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia;

Trematoda:
 Platyhelminthes, Helminthes, Invertebrata, Animalia

ORGN Organism Name
 Muridae (Muridae); Schistosoma mansoni (Trematoda)

ORGN Organism Superterms
 animals; chordates; helminths; invertebrates; mammals; nonhuman mammals; nonhuman vertebrates; platyhelminths; rodents; vertebrates

RN **125978-95-2 (NITRIC OXIDE SYNTHASE)**

L23 ANSWER 1 OF 7 BIOSIS COPYRIGHT 2001 BIOSIS

AN 2001:47391 BIOSIS

DN PREV200100047391

TI Recombinant human IL-12 promotes the anti-tumor activity of human tumor-infiltrating lymphocytes (TIL) through the induction of IFN-gamma and iNOS in a human tumor/TIL SCID mouse xenograft model.

AU Hess, S. D. (1); Egilmez, N. K. (1); Jong, Y. S.; Chen, F.-A. (1); Anderson, T. M. (1); Mathiowitz, E.; Bankert, R. B. (1)

CS (1) Roswell Park Cancer Institute, Buffalo, NY, 14263 USA

SO FASEB Journal, (April 20, 2000) Vol. 14, No. 6, pp. A1007. print.

Meeting Info.: Joint Annual Meeting of the American Association of Immunologists and the Clinical Immunology Society Seattle, Washington, USA

May 12-16, 2000

ISSN: 0892-6638.

DT Conference

LA English

SL English

IT Major Concepts
 Endocrine System (Chemical Coordination and Homeostasis); Immune System (Chemical Coordination and Homeostasis); Tumor Biology

IT Parts, Structures, & Systems of Organisms

tumor-infiltrating lymphocytes: anti-tumor activity, blood and lymphatics, immune system

IT Chemicals & Biochemicals
 IFN-gamma [interferon-gamma]: induction; **IL-12** [**interleukin-12**]: recombinant; N-nitro-L-arginine methyl ester [**L-NAME**]: iNOS inhibitor; iNOS [inducible nitric oxide synthase]; nitric oxide

IT Miscellaneous Descriptors
 human tumor/tumor-infiltrating lymphocyte xenograft model; tumor microenvironment; tumor suppression; Meeting Abstract

ORGN Super Taxa
 Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia;
 Muridae:
 Rodentia, Mammalia, Vertebrata, Chordata, Animalia

ORGN Organism Name
 SCID mouse [severe combined immunodeficiency mouse] (Muridae): animal model; human (Hominidae)

ORGN Organism Superterms
 Animals; Chordates; Humans; Mammals; Nonhuman Mammals; Nonhuman Vertebrates; Primates; Rodents; Vertebrates

RN 50903-99-6 (N-NITRO-L-ARGININE METHYL ESTER)
 50903-99-6 (**L-NAME**)
 10102-43-9 (NITRIC OXIDE)

L23 ANSWER 2 OF 7 BIOSIS COPYRIGHT 2001 BIOSIS
 AN 2000:132853 BIOSIS
 DN PREV200000132853
 TI The potentiated antileukemic effects of doxorubicin and **interleukin-12** combination are not dependent on nitric oxide production.

AU Zagozdzon, Radoslaw (1); Giermasz, Adam; Golab, Jakub; Stoklosa, Tomasz; Jalili, Ahmad; Jakobisiak, Marek

CS (1) Department of Immunology, Institute of Biostructure, Medical University of Warsaw, Chalubinskiego 5, 02-004, Warsaw Poland

SO Cancer Letters., (Dec. 1, 1999) Vol. 147, No. 1-2, pp. 67-75.
 ISSN: 0304-3835.

DT Article
 LA English
 SL English

AB In our recent study we described a significant antileukemic efficacy of a combination therapy with **interleukin-12** (**IL-12**) and doxorubicin (DOX) in the L1210 leukemia model. This therapeutic effect was abrogated by elimination of activated macrophages. Activated macrophages produce a variety of factors that can contribute to the elimination of tumor cells in vivo, including proteases, TNF, reactive oxygen intermediates, and nitric oxide (NO). Based on the results of previous reports, the contribution of NO in potentiated antileukemic effects of **IL-12** + DOX combination seemed to be highly possible. Both DOX and **IL-12** given alone increased the production of NO by peritoneal macrophages, however, macrophages derived from the mice treated with the combination of those agents produced significantly less NO than macrophages from **IL-12**-alone-treated mice. Production of NO by spleen macrophages after **IL-12** + DOX treatment was higher than it was in controls, **IL-12**-alone-or DOX-alone-treated groups. In serum, concentrations of NOx- in **IL-12**- or **IL**

-12 + DOX-treated mice were significantly higher in comparison with controls, however not significantly different from each other. Addition of **L-NAME** treatment to the **IL-12** + DOX therapy in leukemia-bearing mice did not significantly change the antileukemic efficacy of this therapy. Thus, our results indicate that the augmented antileukemic effects of **IL-12** + DOX combination therapy in L1210 model are NO-independent. Therefore, further studies on the possible mechanisms of potentiated antileukemic activity of combination of **IL-12** and DOX would be worth pursuing.

IT Major Concepts
Pharmacology; Tumor Biology

IT Parts, Structures, & Systems of Organisms
macrophage: blood and lymphatics, immune system

IT Diseases
leukemia: blood and lymphatic disease, neoplastic disease

IT Chemicals & Biochemicals
doxorubicin: antineoplastic - drug, combination therapy;
interleukin-12: antineoplastic - drug, combination
therapy; nitric oxide: production; reactive oxygen intermediates;

tumor
necrosis factor

IT Alternate Indexing
Leukemia (MeSH)

IT Methods & Equipment
chemoimmunotherapy: therapeutic method

ORGN Super Taxa
Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia

ORGN Organism Name
L1210 cell line (Muridae): animal model; mouse (Muridae)

ORGN Organism Superterms
Animals; Chordates; Mammals; Nonhuman Mammals; Nonhuman Vertebrates;
Rodents; Vertebrates

RN 23214-92-8 (DOXORUBICIN)
10102-43-9 (NITRIC OXIDE)

L23 ANSWER 3 OF 7 BIOSIS COPYRIGHT 2001 BIOSIS

AN 1999:232593 BIOSIS

DN PREV199900232593

TI CD40 ligation prevents Trypanosoma cruzi infection through
interleukin-12 upregulation.

AU Chaussabel, Damien; Jacobs, Frederique; De Jonge, Jan; De Veerman,
Marijke; Carlier, Yves; Thielemans, Kris; Goldman, Michel; Vray, Bernard
(1)

CS (1) Laboratoire d'Immunologie Experimentale, Faculte de Medecine,
Universite Libre de Bruxelles, route de Lennik, B-1070, Brussels Belgium

SO Infection and Immunity, (April, 1999) Vol. 67, No. 4, pp. 1929-1934.
ISSN: 0019-9567.

DT Article

LA English

SL English

AB Because of the critical role of the CD40-CD40 ligand (CD40L) pathway in
the induction and effector phases of immune responses, we investigated
the effects of CD40 ligation on the control of Trypanosoma cruzi infection.
First, we observed that supernatants of murine spleen cells stimulated by
CD40L-transfected 3T3 fibroblasts (3T3-CD40L transfectants) prevent the

infection of mouse peritoneal macrophages (MPM) by *T. cruzi*. This phenomenon depends on de novo production of nitric oxide (NO) as it is prevented by the addition of N-nitro-L-arginine methyl ester, a NO synthase inhibitor. NO production requires interleukin (IL)-12-mediated gamma interferon (IFN-gamma) and tumor necrosis factor alpha (TNF-alpha) synthesis as demonstrated by inhibition experiments using neutralizing anti-IL-12, anti-IFN-gamma, and anti-TNF-alpha monoclonal antibodies (MAb). We found that an activating anti-CD40 MAb also directly stimulates IFN-gamma-activated MPM to produce NO and thereby to control *T. cruzi* infection. To determine the in vivo relevance of these in vitro findings, mice were injected with 3T3-CD40L transfectants or 3T3 control fibroblasts at the time of *T. cruzi* inoculation. We observed that in vivo CD40 ligation dramatically reduced both parasitemia and the mortality rate of *T. cruzi*-infected mice. A reduced parasitemia was still observed when the injection of 3T3-CD40L transfectants was delayed 8 days postinfection. It was abolished by injection of anti-IL-12 MAb. Taken together, these data establish that CD40 ligation facilitates the control of *T. cruzi* infection through a cascade involving IL-12, IFN-gamma, and NO.

IT Major Concepts
Immune System (Chemical Coordination and Homeostasis); Parasitology

IT Parts, Structures, & Systems of Organisms
peritoneal macrophage: blood and lymphatics, immune system; spleen cells: blood and lymphatics, immune system

IT Diseases
Trypanosoma cruzi infection: parasitic disease

IT Chemicals & Biochemicals
gamma interferon; interleukin-12: upregulation; nitric oxide: production; tumor necrosis factor alpha; CD40; CD40 ligand; N-nitro-L-arginine methyl ester: nitric oxide synthase inhibitor

IT Miscellaneous Descriptors
immune response

ORGN Super Taxa
Flagellata: Protozoa, Invertebrata, Animalia; Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia

ORGN Organism Name
murine (Muridae); Trypanosoma cruzi (Flagellata): pathogen; 3T3 cell line (Muridae): murine fibroblast cells

ORGN Organism Superterms
Animals; Chordates; Invertebrates; Mammals; Microorganisms; Nonhuman Mammals; Nonhuman Vertebrates; Protozoans; Rodents; Vertebrates

RN 10102-43-9 (NITRIC OXIDE)
50903-99-6 (N-NITRO-L-ARGININE METHYL ESTER)
125978-95-2 (NITRIC OXIDE SYNTHASE)

L23 ANSWER 4 OF 7 BIOSIS COPYRIGHT 2001 BIOSIS

AN 1999:56046 BIOSIS

DN PREV199900056046

TI Nitric oxide regulates Th1 cell development through the inhibition of IL-12 synthesis by macrophages.

AU Huang, Fang-Ping; Niedbala, Wanda; Wei, Xiao-Qing; Xu, Damo; Feng, Gui-Jie; Robinson, John H.; Lam, Charles; Liew, Foo Y. (1)

CS (1) Dep. Immunol., Univ. Glasgow, Glasgow G11 6NT UK

SO European Journal of Immunology, (Dec., 1998) Vol. 28, No. 12, pp. 4062-4070.

ISSN: 0014-2980.

DT Article

LA English

AB We have previously reported that mice lacking inducible nitric oxide synthase (NOS2) developed enhanced Th1 cell responses. We now investigated

the mechanism by which NO modulates Th1 cells differentiation. Peritoneal macrophages from NOS2-deficient mice infected with *Leishmania major* in vivo or stimulated with IFN-gamma or lipopolysaccharide (LPS) in vitro produced significantly higher levels of IL-12 than those from heterozygous or wild-type mice. A macrophage cell line, J774, produced significant amounts of IL-12 following activation with LPS, or LPS plus IFN-gamma. This could be markedly enhanced by the NOS inhibitor L-NG monomethyl arginine (L-NMMA), but profoundly inhibited by the NO-generating compound S-nitroso-N-acetyl-penicillamine (SNAP). The effect of NO in this system is selective, since SNAP enhanced and L-NMMA decreased TNF-alpha synthesis by LPS-activated J774 cells. The differential effect of NO on IL-12 and TNF-alpha is at the transcriptional level and is activation dependent. Since IL-12 is a major inducer of Th1 cells which produce IFN-gamma that can activate macrophages to produce IL-12, our data demonstrate that NO can be an inhibitor of this feedback loop, preventing the excessive amplification of Th1 cells which are implicated in a range of immunopathologies.

IT Major Concepts

Biochemistry and Molecular Biophysics; Immune System (Chemical Coordination and Homeostasis); Parasitology

IT Parts, Structures, & Systems of Organisms

peritoneal macrophage: blood and lymphatics, immune system

IT Chemicals & Biochemicals

interferon gamma; lipopolysaccharide; nitric oxide; nitric oxide synthase; tumor necrosis factor-alpha; IL-12 [interleukin-12]; L-N G monomethyl arginine: nitric oxide synthase inhibitor; S-nitroso-N-acetyl-penicillamine: nitric oxide generating compound

IT Miscellaneous Descriptors

Th1 cell response

ORGN Super Taxa

Flagellata: Protozoa, Invertebrata, Animalia; Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia

ORGN Organism Name

mouse (Muridae); J774 cell line (Muridae); *Leishmania major* (Flagellata): parasite

ORGN Organism Superterms

Animals; Chordates; Invertebrates; Mammals; Microorganisms; Nonhuman Mammals; Nonhuman Vertebrates; Protozoans; Rodents; Vertebrates

RN 10102-43-9 (NITRIC OXIDE)

125978-95-2 (NITRIC OXIDE SYNTHASE)

79032-48-7 (S-NITROSO-N-ACETYL-PENICILLAMINE)

74-79-3Q (ARGININE)

7200-25-1Q (ARGININE)

L23 ANSWER 5 OF 7 BIOSIS COPYRIGHT 2001 BIOSIS

AN 1999:41234 BIOSIS

DN PREV199900041234

TI Collagen deposition in a non-fibrotic lung granuloma model after nitric

oxide inhibition.

AU Hogaboam, Cory M. (1); Gallinat, Chad S.; Bone-Larson, Cynthia; Chensue, Stephen W.; Lukacs, Nicholas W.; Strieter, Robert M.; Kunkel, Steven L.

CS (1) Dep. Pathol., Univ. Michigan Med. Sch., 1301 Catherine Road, Ann Arbor, MI 48109-0602 USA

SO American Journal of Pathology, (Dec., 1998) Vol. 153, No. 6, pp. 1861-1872.
ISSN: 0002-9440.

DT Article

LA English

AB Recent studies support the concept that pulmonary granulomatous inflammation directed by interferon (IFN)-gamma, interleukin (IL)-12, and nitric oxide usually resolves in the absence of fibrosis. To determine whether nitric oxide participates in modulating the fibrotic response during the development of pulmonary granulomas in response to purified protein derivative (PPD), mice presensitized to PPD received daily intraperitoneal injections of NG-nitro-D-arginine-methyl ester (D-NAME), N-nitro-L-arginine-methyl ester (L-NAME), or aminoguanidine after delivery of PPD-coated beads to the lungs. Eight days later, morphometric analysis of lung granulomas revealed that L-NAME-treated mice when challenged with PPD in vitro for 36 hours had the largest pulmonary granulomas and the greatest collagen deposition among the treated groups. In addition, equivalent numbers of dispersed lung cells from L-NAME- and aminoguanidine-treated mice produced significantly higher levels of IL-4, monocyte chemoattractant protein (MCP)-1, and macrophage inflammatory protein (MIP)-1 α and significantly lower levels of eotaxin compared with D-NAME-treated mice. Cultures of dispersed lung cells from L-NAME-treated mice also produced significantly more IL-10 and less IL-12 compared with similar numbers of dispersed lung cells from D-NAME-treated mice. Cultures of isolated lung fibroblasts from L-NAME-treated mice expressed higher levels of C-C chemokine receptor 2 (CCR2) and CCR3 mRNA and contained less MCP-1 and eotaxin protein than a similar number of fibroblasts from D-NAME-treated mice. Thus, nitric oxide appears to regulate the deposition of extracellular matrix in lung granulomas through the modulation of the cytokine and chemokine profile of these lesions. Alterations in the cytokine, chemokine, and procollagen profile of this lesion may be a direct effect of nitric oxide on the pulmonary fibroblast and provide an important signal for regulating fibroblast activity during the evolution of chronic lung disease.

IT Major Concepts
Respiratory System (Respiration)

IT Parts, Structures, & Systems of Organisms
lungs: respiratory system

IT Diseases
non-fibrotic lung granuloma: respiratory system disease

IT Chemicals & Biochemicals
collagen; interferon-gamma; interleukin-10; interleukin-12; interleukin-4; macrophage inflammatory protein-1 α ; monocyte chemoattractant protein-1; nitric oxide; purified protein derivative

ORGN Super Taxa
Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia

ORGN Organism Name
 mouse (Muridae): model
 ORGN Organism Superterms
 Animals; Chordates; Mammals; Nonhuman Mammals; Nonhuman Vertebrates;
 Rodents; Vertebrates
 RN 10102-43-9 (NITRIC OXIDE)

L23 ANSWER 6 OF 7 BIOSIS COPYRIGHT 2001 BIOSIS
 AN 1998:496780 BIOSIS
 DN PREV199800496780
 TI Increased nitric oxide (NO) production by antigen-presenting dendritic cells is responsible for low allogeneic mixed leucocyte reaction (MLR) in primary biliary cirrhosis (PBC.
 AU Yamamoto, K. (1); Fazle Akbar, S. M.; Masumoto, T.; Onji, M.
 CS (1) Third Dep. Intern. Med., Ehime Univ. Sch. Med., Shigenobu-Cho, Ehime 791-0295 Japan
 SO Clinical and Experimental Immunology, (Oct., 1998) Vol. 114, No. 1, pp. 94-101.
 ISSN: 0009-9104.
 DT Article
 LA English
 AB The levels of blastogenesis in allogeneic MLR containing T cells from one normal volunteer and irradiated dendritic cells from 29 patients with PBC,
 17 patients with chronic hepatitis type C (CH-C) and 22 allogeneic normal controls were compared to see if there is any role of antigen-presenting cells (APC) in the pathogenesis of PBC. The stimulatory capacity of dendritic cells from PBC was significantly lower compared with that of dendritic cells from CH-C ($P < 0.05$) and normal controls ($P < 0.05$), which could not be attributable either to the levels of expression of surface molecules, such as HLA-DR and CD86 on dendritic cells, or to the levels of
 of cytokines, such as IL-10 and IL-12. Significantly higher levels of NO were seen in the allogeneic MLR supernatants containing dendritic cells from PBC compared with the supernatants from cultures containing dendritic cells from CH-C ($P < 0.001$) or normal controls
 ($P < 0.001$). Moreover, dendritic cells from PBC produced 10 times more NO compared with dendritic cells from CH-C and normal controls (21.9 ± 2.8 μ M versus 1.6 ± 0.3 μ M and 1.6 ± 0.3 μ M, respectively; $P < 0.001$). The addition of NG-monomethyl-L-arginine monoacetate (LNMMA), a known inhibitor of NO in allogeneic MLR containing dendritic cells from PBC, resulted in a significant decrease of NO and increase of blastogenesis. The selective impairment of dendritic cell function, increased production of NO by dendritic cells and restoration of blastogenesis using NO inhibitor in PBC have suggested a role for NO and dysfunction of
 dendritic cells in the pathogenesis of PBC. This inspires optimism that modulating the function of dendritic cells and controlling NO production, an
 improved therapeutic approach, might be planned for PBC.

IT Major Concepts
 Digestive System; Immune System (Chemical Coordination and Homeostasis)
 IT Parts, Structures, & Systems of Organisms
 dendritic cell: antigen-presenting, immune system
 IT Diseases

primary biliary cirrhosis: digestive system disease, pathogenesis

IT Chemicals & Biochemicals
interleukin-10; interleukin-12; nitric oxide:
production; CD86; HLA-DR; N-G-monomethyl-L-arginine

IT Miscellaneous Descriptors
mixed leukocyte reaction: allogeneic, low

ORGN Super Taxa
Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia

ORGN Organism Name
human (Hominidae)

ORGN Organism Superterms
Animals; Chordates; Humans; Mammals; Primates; Vertebrates

RN 10102-43-9 (NITRIC OXIDE)
17035-90-4 (N-G-MONOMETHYL-L-ARGININE)

L23 ANSWER 7 OF 7 BIOSIS COPYRIGHT 2001 BIOSIS

AN 1996:77379 BIOSIS

DN PREV199698649514

TI Production of nitric oxide (NO) is not essential for protection against acute *Toxoplasma gondii* infection in IRF-1-/- mice.

AU Khan, Imtiaz A. (1); Matsuura, Tadashi; Fonseka, Sujeewa; Kasper, Lloyd H.

CS (1) Dep. Med., Dartmouth Medical School, Vail 212, Hanover, NH 03755 USA

SO Journal of Immunology, (1996) Vol. 156, No. 2, pp. 636-643.
ISSN: 0022-1767.

DT Article

LA English

AB Production of nitric oxide (NO) by macrophages is important for the killing of intracellular pathogens. IFN-gamma and LPS stimulate NO production by transcriptional up-regulation of inducible nitric oxide synthetase (iNOS). In the present study we used mice with a targeted disruption of the IFN regulatory factor-1 gene (IRF-1-/-) to investigate the importance of NO in the host immune response against *Toxoplasma gondii*, a major cause of infection in newborns and those with AIDS. IRF-1-/- mice were more susceptible to acute *Toxoplasma* infection, and treatment with either exogenous IFN-gamma or in vivo neutralization of endogenous IFN-gamma had little effect on their susceptibility to infection. However, administration of exogenous IL-12 was able to prolong survival even when IFN-gamma was depleted. An in vivo depletion study suggested that the mechanism of this protective response is mediated in part by CD4+ T cells. The administration of IL-12 could not overcome the inhibition of lymphoproliferative response in T. *gondii*-infected mice and treatment with N-monomethyl-L-arginine (L-NMMA), a nitric oxide synthase (iNOS) antagonist in vitro was unable to reverse the immunosuppression. In response to *Toxoplasma* infection, splenocytes from IRF-1-/- mice exhibited increased production of IL-10 as well as a 30-fold increase in its message expression. These studies indicate that NO may not be essential for host immunity to the parasite, and moreover that IL-12 appears to induce an IFN-gamma-independent mechanism of protection against this opportunistic pathogen.

IT Major Concepts
Biochemistry and Molecular Biophysics; Blood and Lymphatics (Transport and Circulation); Cell Biology; Genetics; Immune System (Chemical Coordination and Homeostasis); Metabolism; Parasitology

IT Chemicals & Biochemicals
NITRIC OXIDE

IT Miscellaneous Descriptors
INTERFERON REGULATORY FACTOR-1 GENE; INTERLEUKIN-12
; OPPORTUNISTIC PATHOGEN; PARASITE HOST IMMUNITY
ORGN Super Taxa
Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia; Sporozoa:
Invertebrata, Protozoa, Animalia
ORGN Organism Name
Muridae (Muridae); Toxoplasma gondii (Sporozoa)
ORGN Organism Superterms
animals; chordates; invertebrates; mammals; microorganisms; nonhuman
mammals; nonhuman vertebrates; protozoans; rodents; vertebrates
RN 10102-43-9 (NITRIC OXIDE)

=> fil medline

FILE 'MEDLINE' ENTERED AT 11:23:48 ON 22 FEB 2001

FILE LAST UPDATED: 27 OCT 2000 (20001027/UP). FILE COVERS 1960 TO DATE.

MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the MeSH 2000 vocabulary. Enter HELP THESAURUS for details.

The OLDMEDLINE file segment now contains data from 1958 through 1965. Enter HELP CONTENT for details.

Left, right, and simultaneous left and right truncation are available in the Basic Index. See HELP SFIELDS for details.

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=> d his 11-112

(FILE 'MEDLINE' ENTERED AT 11:13:00 ON 22 FEB 2001)

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      DEL HIS Y
L1      0 S INTERLEUKIN'-'12CT
L2      2762 S INTERLEUKIN'-'12/CT
L3      21589 S NITRIC OXIDE/CT
L4      10800 S NITRIC'-'OXIDE SYNTHASE+NT/CT
L5      27423 S L3 OR L4
L6      6321 S L5 (L) AI./CT
L7      21 S L6 AND L2
      E NG-NITROARGININE METHYL ESTER/CT
      E E3+ALL
      E L-NMMA/CT
      E E3+ALL
L8      2943 S NG'-'NITROARGININE METHYL ESTER/CT
L9      1269 S OMEGA'-'N'-'METHYLARGININE/CT
L10     4098 S L8 OR L9
L11     6 S L10 AND L2
L12     23 S L11 OR L7
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=> d .med 112 1-23

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L12  ANSWER 1 OF 23  MEDLINE
AN   2000123487      MEDLINE
DN   20123487
TI   The potentiated antileukemic effects of doxorubicin and interleukin-12
      combination are not dependent on nitric oxide production.
AU   Zagozdzon R; Giermasz A; Golab J; Stoklosa T; Jalili A; Jakobisiak M
CS   Department of Immunology, Institute of Biostructure, Medical University
of   Warsaw, Poland.. rzagozd@ib.amwaw.edu.pl
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SO CANCER LETTERS, (1999 Dec 1) 147 (1-2) 67-75.
Journal code: CMX. ISSN: 0304-3835.

CY Ireland

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals; Cancer Journals

EM 200005

EW 20000501

AB In our recent study we described a significant antileukemic efficacy of a combination therapy with interleukin-12 (IL-12) and doxorubicin (DOX) in the L1210 leukemia model. This therapeutic effect was abrogated by elimination of activated macrophages. Activated macrophages produce a variety of factors that can contribute to the elimination of tumor cells in vivo, including proteases, TNF, reactive oxygen intermediates, and nitric oxide (NO). Based on the results of previous reports, the contribution of NO in potentiated antileukemic effects of IL-12 + DOX combination seemed to be highly possible. Both DOX and IL-12 given alone increased the production of NO by peritoneal macrophages, however, macrophages derived from the mice treated with the combination of those agents produced significantly less NO than macrophages from IL-12-alone-treated mice. Production of NO by spleen macrophages after IL-12 + DOX treatment was higher than it was in controls, IL-12-alone or DOX-alone-treated groups. In serum, concentrations of NOx- in IL-12- or IL-12 + DOX-treated mice were significantly higher in comparison with controls, however not significantly different from each other. Addition of L-NAME treatment to the IL-12 + DOX therapy in leukemia-bearing mice did not significantly change the antileukemic efficacy of this therapy. Thus, our results indicate that the augmented antileukemic effects of IL-12 + DOX combination therapy in L1210 model are NO-independent. Therefore, further studies on the possible mechanisms of potentiated antileukemic activity of combination of IL-12 and DOX would be worth pursuing.

CT Check Tags: Animal; Female; Support, Non-U.S. Gov't
Adjuvants, Immunologic: AD, administration & dosage
Antibiotics, Anthracycline: AD, administration & dosage
*Antineoplastic Agents, Combined: TU, therapeutic use
Cells, Cultured
Crosses, Genetic
Doxorubicin: AD, administration & dosage
Drug Synergism
Enzyme Inhibitors: PD, pharmacology
Interleukin-12: AD, administration & dosage
*Leukemia L1210: DT, drug therapy
Leukemia L1210: IM, immunology
*Leukemia L1210: ME, metabolism
Leukemia L1210: PA, pathology
Macrophages, Peritoneal: DE, drug effects
Macrophages, Peritoneal: IM, immunology
Macrophages, Peritoneal: ME, metabolism
Mice
Mice, Inbred C57BL
Mice, Inbred DBA
Neoplasm Transplantation
Nitrates: BL, blood
*Nitric Oxide: BI, biosynthesis
Nitric-Oxide Synthase: AI, antagonists & inhibitors
Nitrites: BL, blood

NG-Nitroarginine Methyl Ester: PD, pharmacology

Spleen: DE, drug effects

Spleen: ME, metabolism

Survival Rate

L12 ANSWER 2 OF 23 MEDLINE

AN 2000103831 MEDLINE

DN 20103831

TI Antifungal type 1 responses are upregulated in IL-10-deficient mice.

AU Del Sero G; Mencacci A; Cenci E; d'Ostiani C F; Montagnoli C; Bacci A; Mosci P; Kopf M; Romani L

CS Department of Experimental Medicine and Biochemical Sciences, University of Perugia, Italy.

SO Microbes Infect, (1999 Dec) 1 (14) 1169-80.

Journal code: DJ1. ISSN: 1286-4579.

CY France

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 200004

EW 20000404

AB C57BL/6 mice are highly resistant to infections caused by *Candida albicans*

and *Aspergillus fumigatus*. To elucidate the role of IL-10 produced by C57BL/6 mice during these infections, parameters of infection and immunity

to it were evaluated in IL-10-deficient and wild-type mice with disseminated or gastrointestinal candidiasis or invasive pulmonary aspergillosis. Unlike parasitic protozoan infection, *C. albicans* or *A. fumigatus* infection did not induce significant acute toxicity in IL-10-deficient mice, who, instead, showed reduced fungal burden and fungal-associated inflammatory responses. The increased resistance to infections as compared to wild-type mice was associated with upregulation of innate and acquired antifungal Th1 responses, such as a dramatically higher production of IL-12, nitric oxide (NO) and TNF-alpha as well as IFN-gamma by CD4+ T cells. Pharmacological inhibition of NO production greatly reduced resistance to gastrointestinal candidiasis, thus pointing to the importance of IL-10-dependent NO regulation at mucosal sites in fungal infections. These results are reminiscent of those obtained in genetically susceptible mice, in which IL-10 administration increased,

and

IL-10 neutralization decreased, susceptibility to *C. albicans* and *A. fumigatus* infections. Collectively, these observations indicate that the absence of IL-10 augments innate and acquired antifungal immunity by upregulating type 1 cytokine responses. The resulting protective Th1 responses lead to a prompt reduction of fungal growth, thus preventing tissue destruction and lethal levels of proinflammatory cytokines.

CT Check Tags: Animal; Female; Male; Support, Non-U.S. Gov't

Antigens, CD4: ME, metabolism

Aspergillus fumigatus

Candida albicans

Enzyme-Linked Immunosorbent Assay

Guanidines: PD, pharmacology

Immunity, Cellular

Immunity, Natural

Inflammation

Interferon Type II: ME, metabolism

Interleukin-10: GE, genetics
 Interleukin-10: ME, metabolism
 *Interleukin-10: PH, physiology
 Interleukin-12: ME, metabolism
 Mice
 Mice, Inbred C57BL
 Mice, Knockout
 *Mycoses: IM, immunology
 Mycoses: MI, microbiology
 Mycoses: PA, pathology
 Nitric Oxide: AI, antagonists & inhibitors
 Nitric Oxide: ME, metabolism
 Nitric-Oxide Synthase: AI, antagonists & inhibitors
 Polymerase Chain Reaction
 RNA, Messenger: AN, analysis
 Th1 Cells: IM, immunology
 *Th1 Cells: ME, metabolism
 Tumor Necrosis Factor: ME, metabolism

L12 ANSWER 3 OF 23 MEDLINE

AN 2000087332 MEDLINE

DN 20087332

TI Role of interferon-gamma and nitric oxide in pulmonary edema and death induced by lipopolysaccharide.

AU Heremans H; Dillen C; Groenen M; Matthys P; Billiau A

CS Laboratory of Immunobiology, Rega Institute, University of Leuven, Faculty

of Medicine, Leuven, Belgium.. Hubertine.Heremans@rega.kuleuven.ac.be

SO AMERICAN JOURNAL OF RESPIRATORY AND CRITICAL CARE MEDICINE, (2000 Jan) 161

(1) 110-7.

Journal code: BZS. ISSN: 1073-449X.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Abridged Index Medicus Journals; Priority Journals

EM 200005

EW 20000501

AB Mice given lipopolysaccharide (LPS) intravenously developed lung edema, which was maximum after 6 h. Tumor necrosis factor, interleukin 12 (IL-12), IL-6, and interferon-gamma (IFN-gamma) appeared in the serum,

and levels of nitrogen oxide (NO) derivatives were increased in serum and bronchoalveolar fluid. Mice pretreated with neutralizing anti-IFN-gamma antibodies had lower serum levels of IFN-gamma, and fewer died. However, levels of other cytokines and NO derivatives as well as lung edema were unchanged. If IFN-gamma and LPS were given together, pulmonary edema was less, but levels of cytokines and NO derivatives in serum were raised,

and the mortality was greater. IFN-gamma receptor knockout mice had more edema

after LPS, but were less sensitive to the lethal effects. Treatment with anti-IL-12 antibody inhibited IFN-gamma induction and reduced mortality, but had no effect on the lung edema; exogenous IL-12 also failed to affect

edema, but boosted serum cytokine levels and increased the mortality. Aminoguanidine, an inhibitor of NO synthase, protected against pulmonary

edema, but did not modify the lethal effects of LPS. Clearly, in this model, early pulmonary edema and lethality are not directly related, and induced IFN-gamma has no role in causing early lung edema, but augments other events that result in death.

CT Check Tags: Animal; Comparative Study; Female; Support, Non-U.S. Gov't
 Bronchoalveolar Lavage Fluid: CH, chemistry
 Disease Models, Animal
 Enzyme Inhibitors: PD, pharmacology
 Guanidines: PD, pharmacology
 Interferon-alpha: PD, pharmacology
 *Interferon-alpha: PH, physiology
Interleukin-12: ME, metabolism
 Interleukin-6: ME, metabolism
 *Lipopolysaccharides: TO, toxicity
 Mice
 Mice, Inbred Strains
 *Nitric Oxide: PH, physiology
Nitric-Oxide Synthase: AI, antagonists & inhibitors
 Pulmonary Edema: CI, chemically induced
 *Pulmonary Edema: ME, metabolism
 Pulmonary Edema: MO, mortality
 Pulmonary Edema: PC, prevention & control
 *Serratia marcescens
 Tumor Necrosis Factor: ME, metabolism

L12 ANSWER 4 OF 23 MEDLINE

AN 1999388002 MEDLINE

DN 99388002

TI Effects of nitric oxide on the induction and differentiation of Th1 cells.

AU Niedbala W; Wei X Q; Piedrafita D; Xu D; Liew F Y

CS Department of Immunology, University of Glasgow, Glasgow, GB.

SO EUROPEAN JOURNAL OF IMMUNOLOGY, (1999 Aug) 29 (8) 2498-505.

Journal code: EN5. ISSN: 0014-2980.

CY GERMANY: Germany, Federal Republic of

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals; Cancer Journals

EM 199911

EW 19991104

AB We have previously shown that mice lacking inducible NO synthase are markedly more susceptible to Leishmania major infection but developed a significantly enhanced Th1 cell response compared with wild-type mice. Furthermore, at high concentrations, NO inhibited IL-12 synthesis by activated macrophages, thereby indirectly suppressing the expansion of

Th1 cells. We report here that at low concentrations, NO selectively enhanced the induction of Th1 cells and had no effect on Th2 cells. NO exerted

this effect in synergy with IL-12 during Th1 cell differentiation and had no effect on fully committed Th1 cells. NO appears to affect CD4(+) T cells directly and not at the antigen-presenting cells. These results therefore provide an additional pathway by which NO modulates the immune response and contributes to the homeostasis of the immune system.

CT Check Tags: Animal; Support, Non-U.S. Gov't

Cell Differentiation: DE, drug effects

Clone Cells

CD4-Positive T-Lymphocytes: CY, cytology
 CD4-Positive T-Lymphocytes: DE, drug effects
 CD4-Positive T-Lymphocytes: IM, immunology
 Drug Synergism
 Enzyme Inhibitors: PD, pharmacology
Interleukin-12: AD, administration & dosage
Interleukin-12: PD, pharmacology
 Leishmania major
 Leishmaniasis, Cutaneous: ET, etiology
 Leishmaniasis, Cutaneous: IM, immunology
 Lymphocyte Transformation
 Lysine: AA, analogs & derivatives
 Lysine: PD, pharmacology
 Mice
 Mice, Inbred BALB C
 Mice, Knockout
 Nitric Oxide: AD, administration & dosage
 *Nitric Oxide: PD, pharmacology
 Nitric Oxide Donors: PD, pharmacology
Nitric-Oxide Synthase: AI, antagonists & inhibitors
 Nitric-Oxide Synthase: DF, deficiency
 Nitric-Oxide Synthase: GE, genetics
 Penicillamine: AA, analogs & derivatives
 Penicillamine: PD, pharmacology
 Th1 Cells: CY, cytology
 *Th1 Cells: DE, drug effects
 *Th1 Cells: IM, immunology

L12 ANSWER 5 OF 23 MEDLINE
 AN 1999369977 MEDLINE
 DN 99369977
 TI Bruton's tyrosine kinase deficiency in macrophages inhibits nitric oxide generation leading to enhancement of IL-12 induction.
 AU Mukhopadhyay S; George A; Bal V; Ravindran B; Rath S
 CS National Institute of Immunology, New Delhi, India.
 SO JOURNAL OF IMMUNOLOGY, (1999 Aug 15) 163 (4) 1786-92.
 Journal code: IFB. ISSN: 0022-1767.
 CY United States
 DT Journal; Article; (JOURNAL ARTICLE)
 LA English
 FS Abridged Index Medicus Journals; Priority Journals; Cancer Journals
 EM 199911
 EW 19991102
 AB We show that macrophages of X-linked immunodeficient mice with a mutant nonfunctional Bruton's tyrosine kinase produce less NO than wild-type macrophages in response to a variety of stimuli. Induction of the inducible NO synthase (iNOS) protein, the transcription factor IFN regulatory factor-1 involved in iNOS expression, and the transcription factor STAT-1 involved in regulating IFN regulatory factor-1 induction are all poorer in X-linked immunodeficient than in wild-type macrophages. On the other hand, induction of IL-12 is higher in X-linked immunodeficient than in wild-type macrophages. Macrophage IL-12 induction is enhanced by iNOS inhibitors such as aminoguanidine and thiocitrulline and is inhibited by NO generation via sodium nitroprusside. There is relative enhancement of IFN-gamma production by immune T cells from mice immunized under

aminoguanidine cover. Our data thus suggest that Bruton's tyrosine kinase participates in signaling for iNOS induction via IFN regulatory factor-1 in macrophages and that NO is an inhibitor of IL-12 induction.

CT Check Tags: Animal; Support, Non-U.S. Gov't

Chickens

Conalbumin: AD, administration & dosage

Conalbumin: IM, immunology

DNA-Binding Proteins: BI, biosynthesis

DNA-Binding Proteins: GE, genetics

Enzyme Inhibitors: PD, pharmacology

Guanidines: PD, pharmacology

Immunologic Deficiency Syndromes: EN, enzymology

Immunologic Deficiency Syndromes: GE, genetics

Interleukin-12: AI, antagonists & inhibitors

***Interleukin-12: BI, biosynthesis**

Lymphocyte Transformation: GE, genetics

*Macrophages, Peritoneal: EN, enzymology

Macrophages, Peritoneal: IM, immunology

Macrophages, Peritoneal: ME, metabolism

Mice

Mice, Inbred CBA

Mice, Mutant Strains

***Nitric Oxide: AI, antagonists & inhibitors**

*Nitric Oxide: BI, biosynthesis

Nitric Oxide: PD, pharmacology

Nitric-Oxide Synthase: BI, biosynthesis

Nitric-Oxide Synthase: DF, deficiency

Nitric-Oxide Synthase: GE, genetics

Phosphoproteins: BI, biosynthesis

Phosphoproteins: GE, genetics

*Protein-Tyrosine Kinase: DF, deficiency

*Protein-Tyrosine Kinase: GE, genetics

T-Lymphocytes: IM, immunology

Trans-Activators: BI, biosynthesis

Trans-Activators: GE, genetics

L12 ANSWER 6 OF 23 MEDLINE

AN 1999255858 MEDLINE

DN 99255858

TI Requirement for type 2 NO synthase for IL-12 signaling in innate immunity [published erratum appears in Science 1999 Jun 11;284(5421):1776].

AU Diefenbach A; Schindler H; Rollinghoff M; Yokoyama W M; Bogdan C

CS Institut fur Klinische Mikrobiologie, Immunologie und Hygiene, Universitat

Erlangen, Wasserturmstrasse 3, D-91054 Erlangen, Germany.

SO SCIENCE, (1999 May 7) 284 (5416) 951-5.

Journal code: UJ7. ISSN: 0036-8075.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Cancer Journals; Priority Journals

EM 199908

AB Interleukin-12 (IL-12) and type 2 NO synthase (NOS2) are crucial for defense against bacterial and parasitic pathogens, but their relationship in innate immunity is unknown. In the absence of NOS2 activity, IL-12 was unable to prevent spreading of Leishmania parasites, did not stimulate natural killer (NK) cells for cytotoxicity or interferon-gamma (IFN-gamma)

release, and failed to activate Tyk2 kinase and to tyrosine phosphorylate Stat4 (the central signal transducer of IL-12) in NK cells. Activation of Tyk2 in NK cells by IFN-alpha/beta also required NOS2. Thus, NOS2-derived NO is a prerequisite for cytokine signaling and function in innate immunity.

CT Check Tags: Animal; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
 Cells, Cultured
 Cyclic GMP: ME, metabolism
 Cytotoxicity, Immunologic
 DNA-Binding Proteins: ME, metabolism
 Enzyme Activation
 Enzyme Inhibitors: PD, pharmacology
 Immunity, Natural
 Interferon Type II: BI, biosynthesis
 Interferon Type II: GE, genetics
 Interferons: PD, pharmacology
 Interleukin-12: PD, pharmacology
 *Interleukin-12: PH, physiology
 *Killer Cells, Natural: IM, immunology
 Killer Cells, Natural: ME, metabolism
 *Leishmania major
 *Leishmaniasis, Cutaneous: IM, immunology
 Leishmaniasis, Cutaneous: ME, metabolism
 Lysine: AA, analogs & derivatives
 Lysine: PD, pharmacology
 Mice
 Mice, Inbred BALB C
 Mice, Inbred C57BL
 Nitric Oxide: ME, metabolism
 Nitric-Oxide Synthase: AI, antagonists & inhibitors
 *Nitric-Oxide Synthase: ME, metabolism
 Phosphorylation
 Protein-Tyrosine Kinase: ME, metabolism
 Proteins: ME, metabolism
 *Signal Transduction
 Trans-Activators: ME, metabolism
 Up-Regulation (Physiology)

L12 ANSWER 7 OF 23 MEDLINE

AN 1999244892 MEDLINE

DN 99244892

TI Different doses of adenoviral vector expressing IL-12 enhance or depress the immune response to a coadministered antigen: the role of nitric oxide.

AU Lasarte J J; Corrales F J; Casares N; Lopez-Diaz de Cerio A; Qian C; Xie X; Borrás-Cuesta F; Prieto J

CS Department of Internal Medicine, Medical School and University Clinic, University of Navarra, Pamplona, Spain.

SO JOURNAL OF IMMUNOLOGY, (1999 May 1) 162 (9) 5270-7.
 Journal code: IFB. ISSN: 0022-1767.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Abridged Index Medicus Journals; Priority Journals; Cancer Journals

EM 199907

EW 19990704

AB Joint immunization with two recombinant adenoviruses, one expressing

hepatitis C virus (HCV) core and E1 proteins and another expressing IL-12 (RAdIL-12), strongly potentiates cellular immune response against HCV Ags in BALB/c mice when RAdIL-12 was used at doses of 1×10^5 – 1×10^7 plaque-forming units. However, cellular immunity against HCV Ags was abolished when higher doses (1×10^8 plaque-forming units) of RAdIL-12 were used. This immunosuppressive effect was associated with marked elevation of IFN-gamma and nitric oxide in the serum and increased cell apoptosis in the spleen. Administration of N-nitro-L -arginine methyl ester (L-NAME), an inhibitor of nitric oxide synthase, to mice that received high doses of RAdIL-12 was lethal, whereas no apparent systemic toxicity by L -NAME was observed in those immunized with lower doses of the adenovirus. Interestingly, in mice immunized with recombinant adenovirus expressing core and E1 proteins of HCV in combination with RAdIL-12 at low doses (1×10^7 plaque-forming units), L -NAME inhibited T cell proliferation and CTL activity in response to HCV Ags and also production of Abs against adenoviral proteins. In conclusion, gene transfer of IL-12 can increase or abolish cell immunity against an Ag depending of the dose of the vector expressing the cytokine. IL-12 stimulates the synthesis of NO which is needed for the immunostimulating effects of IL-12, but apoptosis of T cells and immunosuppression ensues when IFN-gamma and NO are generated at very high concentrations.

CT Check Tags: Animal; Support, Non-U.S. Gov't

*Adenoviridae: GE, genetics

*Adenoviridae: IM, immunology

Antibodies, Viral: BI, biosynthesis

Antigens, Viral: AD, administration & dosage

*Antigens, Viral: IM, immunology

Apoptosis: IM, immunology

Defective Viruses: GE, genetics

Defective Viruses: IM, immunology

Dose-Response Relationship, Immunologic

Epitopes, T-Lymphocyte: AD, administration & dosage

Epitopes, T-Lymphocyte: IM, immunology

Gene Expression Regulation: IM, immunology

Gene Transfer

*Genetic Vectors: AD, administration & dosage

Genetic Vectors: CS, chemical synthesis

*Genetic Vectors: IM, immunology

Hepatitis C-Like Viruses: IM, immunology

IgG: BI, biosynthesis

Injections, Intraperitoneal

Interferon Type II: BL, blood

Interleukin-12: BI, biosynthesis

Interleukin-12: BL, blood

*Interleukin-12: GE, genetics

Mice

Mice, Inbred BALB C

Nitric Oxide: BI, biosynthesis

*Nitric Oxide: PH, physiology

NG-Nitroarginine Methyl Ester: AD, administration & dosage

Peritoneal Cavity: CY, cytology

Recombination, Genetic

Spleen: PA, pathology

T-Lymphocytes: DE, drug effects

T-Lymphocytes: IM, immunology

T-Lymphocytes: ME, metabolism

T-Lymphocytes, Cytotoxic: IM, immunology

Viral Core Proteins: GE, genetics
 Viral Core Proteins: IM, immunology
 Viral Envelope Proteins: GE, genetics
 Viral Envelope Proteins: IM, immunology

L12 ANSWER 8 OF 23 MEDLINE
 AN 1999128115 MEDLINE
 DN 99128115
 TI Strategies of protection from nitric oxide toxicity in islet inflammation.
 AU Rothe H; Kolb H
 CS Diabetes Research Institute at the Heinrich-Heine University of Dusseldorf, Germany.
 SO JOURNAL OF MOLECULAR MEDICINE, (1999 Jan) 77 (1) 40-4. Ref: 51
 Journal code: B8C. ISSN: 0946-2716.
 CY GERMANY: Germany, Federal Republic of
 DT Journal; Article; (JOURNAL ARTICLE)
 General Review; (REVIEW)
 (REVIEW, TUTORIAL)
 LA English
 FS Priority Journals
 EM 199910
 EW 19991003
 AB Nitric oxide is thought to contribute to beta cell destruction during islet inflammation in animal models of type I diabetes. In vitro, inhibition of inducible nitric oxide synthase protects islet cells from the damaging effects of inflammatory cells or cytokines. However, the administration of several inducible nitric oxide synthase inhibitors to prediabetic animals had variable effects on disease progression. An alternative approach is to prevent the lethal consequences of nitric oxide action at the level of islet cells. We observed that the suppression of poly-(ADP-ribose)-polymerase ensures survival of islet cells exposed to nitric oxide. Cells could also be rendered resistant by the induction of endogenous stress proteins in particular of heat shock protein 70. Nitric oxide is not only a strong cytotoxic agent, but is also able to modulate immune reactions by interfering with Th1/Th2 reactivities. This may occur via induction of the interleukin-12 antagonist IL-12(p40)2. Development of type 1 diabetes is known to be correlated with a shift from a Th2 status during benign insulinitis to a Th1 status during destructive insulinitis. This shift was found dependent on local interleukin-12 gene expression. Indeed, administration of a natural interleukin-12 antagonist suppressed the progression of islet inflammation and concomitant upregulation of the inducible nitric oxide synthase.
 CT Check Tags: Animal; Support, Non-U.S. Gov't
 Diabetes Mellitus, Insulin-Dependent: DT, drug therapy
 Diabetes Mellitus, Insulin-Dependent: IM, immunology
 Diabetes Mellitus, Insulin-Dependent: PA, pathology
 *Diabetes Mellitus, Insulin-Dependent: PP, physiopathology
 Interleukin-12: AI, antagonists & inhibitors
 Interleukin-12: PH, physiology
 Islets of Langerhans: ME, metabolism
 *Islets of Langerhans: PA, pathology
 Mice

Mice, Inbred NOD
 *Nitric Oxide: PH, physiology
Nitric-Oxide Synthase: AI, antagonists & inhibitors
 NAD+ ADP-Ribosyltransferase: ME, metabolism
 T-Lymphocytes: IM, immunology

L12 ANSWER 9 OF 23 MEDLINE
 AN 1999036420 MEDLINE
 DN 99036420
 TI Phlebotomus papatasi sand fly salivary gland lysate down-regulates a Th1, but up-regulates a Th2, response in mice infected with Leishmania major.
 AU Mbow M L; Bleyenbergh J A; Hall L R; Titus R G
 CS Department of Pathology, Colorado State University College of Veterinary Medicine and Biomedical Sciences, Fort Collins 80523-1671, USA.
 NC AI27511-09 (NIAID)
 SO JOURNAL OF IMMUNOLOGY, (1998 Nov 15) 161 (10) 5571-7.
 Journal code: IFB. ISSN: 0022-1767.
 CY United States
 DT Journal; Article; (JOURNAL ARTICLE)
 LA English
 FS Abridged Index Medicus Journals; Priority Journals; Cancer Journals
 EM 199902
 EW 19990204
 AB A vertebrate host becomes infected with Leishmania major when the sand fly vector injects parasites into skin along with saliva. Previous studies showed that salivary gland lysate of the New World sand fly Lutzomyia longipalpis markedly enhanced L. major infection in CBA mice. However, L. major is an Old World parasite transmitted in nature by the Old World sand fly Phlebotomus papatasi. Here we examine the ability of P. papatasi salivary gland lysate to enhance infection (lesion size and parasite burden) by L. major. In addition, we examine the effects of salivary gland lysate on the immune response to L. major by monitoring the levels of cytokine mRNA from the lymph nodes draining cutaneous lesions. We found that P. papatasi salivary gland lysate dramatically exacerbated lesion development in disease-resistant CBA mice. This exacerbation of disease correlated with inhibition of the production of Th1 cytokines and associated factors (IFN-gamma, IL-12, and inducible nitric oxide synthase), but with enhancement of the Th2 cytokine IL-4, whereas no changes in the levels of IL-10 and TGF-beta were noted. Importantly, salivary gland lysate directly up-regulated expression of IL-4 mRNA in mice in the absence of infection with L. major.
 CT Check Tags: Animal; Female; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
 *Down-Regulation (Physiology): IM, immunology
 Interferon Type II: AI, antagonists & inhibitors
 Interferon Type II: BI, biosynthesis
 Interferon Type II: GE, genetics
 Interleukin-10: BI, biosynthesis
 Interleukin-10: GE, genetics
Interleukin-12: AI, antagonists & inhibitors
Interleukin-12: BI, biosynthesis
Interleukin-12: GE, genetics
 Interleukin-4: BI, biosynthesis
 Interleukin-4: GE, genetics

*Leishmania major: IM, immunology
 *Leishmaniasis, Cutaneous: IM, immunology
 Leishmaniasis, Cutaneous: PA, pathology
 Leishmaniasis, Cutaneous: PS, parasitology
 Lymph Nodes: EN, enzymology
 Lymph Nodes: IM, immunology
 Lymph Nodes: ME, metabolism
 Mice
 Mice, Inbred CBA
Nitric-Oxide Synthase: AI, antagonists & inhibitors
 Nitric-Oxide Synthase: BI, biosynthesis
 Nitric-Oxide Synthase: GE, genetics
 *Phlebotomus: IM, immunology
 RNA, Messenger: AI, antagonists & inhibitors
 RNA, Messenger: BI, biosynthesis
 Salivary Glands: CH, chemistry
 *Salivary Glands: IM, immunology
 *Th1 Cells: IM, immunology
 Th1 Cells: ME, metabolism
 *Th2 Cells: IM, immunology
 Th2 Cells: ME, metabolism
 Transforming Growth Factor beta: BI, biosynthesis
 Transforming Growth Factor beta: GE, genetics
 *Up-Regulation (Physiology): IM, immunology

L12 ANSWER 10 OF 23 MEDLINE

AN 1999021681 MEDLINE

DN 99021681

TI Immune suppression by recombinant interleukin (rIL)-12 involves
 interferon

gamma induction of nitric oxide synthase 2 (iNOS) activity: inhibitors of
 NO generation reveal the extent of rIL-12 vaccine adjuvant effect.

AU Koblish H K; Hunter C A; Wysocka M; Trinchieri G; Lee W M

CS Cell and Molecular Biology Graduate Group, Cancer Center, and Institute
 for Human Gene Therapy, School of Medicine, University of Pennsylvania,
 Philadelphia, Pennsylvania 19104, USA.

NC AI-42334-01 (NIAID)

AI-34412 (NIAID)

CA 10815 (NCI)

+

SO JOURNAL OF EXPERIMENTAL MEDICINE, (1998 Nov 2) 188 (9) 1603-10.

Journal code: I2V. ISSN: 0022-1007.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals; Cancer Journals

EM 199902

EW 19990204

AB Recombinant interleukin 12 (IL-12) can profoundly suppress cellular
 immune

responses in mice. To define the underlying mechanism, recombinant murine
 (rm)IL-12 was given to C57BL/6 mice undergoing alloimmunization and found
 to transiently but profoundly suppress in vivo and in vitro allogeneic
 responses and in vitro splenocyte mitogenic responses. Use of

neutralizing

antibodies and genetically deficient mice showed that IFN-gamma (but not
 TNF-alpha) mediated rmIL-12-induced immune suppression. Splenocyte

fractionation studies revealed that adherent cells from rmIL-12-treated mice suppressed the mitogenic response of normal nonadherent cells to concanavalin A and IL-2. Addition of an inhibitor of nitric oxide synthase (NOS) restored mitogenic responses, and inducible (i)NOS-/- mice were not immunosuppressed by rmIL-12. These results support the view that suppression of T cell responses is due to NO produced by macrophages responding to the high levels of IFN-gamma induced by rmIL-12. When a NOS inhibitor was given with rmIL-12 during vaccination of A/J mice with irradiated SCK tumor cells, immunosuppression was averted and the extent of rmIL-12's ability to enhance induction of protective antitumor immunity was revealed. This demonstrates that rmIL-12 is an effective vaccine adjuvant whose efficacy may be masked by its transient immunosuppressive effect.

CT Check Tags: Animal; Female; Support, U.S. Gov't, Non-P.H.S.; Support, U.S. Gov't, P.H.S.

Adjuvants, Immunologic: AD, administration & dosage
 Adjuvants, Immunologic: PD, pharmacology
 Enzyme Induction: DE, drug effects
 Enzyme Inhibitors: PD, pharmacology
 *Immune Tolerance: DE, drug effects
 Immunosuppressive Agents: AD, administration & dosage
 Immunosuppressive Agents: PD, pharmacology
 Interferon Type II: GE, genetics
 *Interferon Type II: ME, metabolism
 Interleukin-12: AD, administration & dosage
 *Interleukin-12: PD, pharmacology
 Lymphocyte Transformation: DE, drug effects
 Mice
 Mice, Inbred A
 Mice, Inbred C57BL
 Mice, Knockout
 Nitric Oxide: IM, immunology
 Nitric-Oxide Synthase: AI, antagonists & inhibitors
 *Nitric-Oxide Synthase: BI, biosynthesis
 Nitric-Oxide Synthase: GE, genetics
 NG-Nitroarginine Methyl Ester: PD, pharmacology
 Recombinant Proteins: AD, administration & dosage
 Recombinant Proteins: PD, pharmacology
 T-Lymphocytes: DE, drug effects
 T-Lymphocytes: IM, immunology
 Vaccines: AD, administration & dosage

L12 ANSWER 11 OF 23 MEDLINE
 AN 1998393445 MEDLINE
 DN 98393445
 TI Vasoactive intestinal peptide inhibits IL-12 and nitric oxide production in murine macrophages.
 AU Xin Z; Sriram S
 CS Vanderbilt University Medical Center, Nashville, TN, USA.
 SO JOURNAL OF NEUROIMMUNOLOGY, (1998 Aug 14) 89 (1-2) 206-12.
 Journal code: HSO. ISSN: 0165-5728.
 CY Netherlands
 DT Journal; Article; (JOURNAL ARTICLE)
 LA English

FS Priority Journals
 EM 199811
 EW 19981102
 AB Vasoactive intestinal peptide (VIP) is a naturally occurring neuropeptide widely distributed in the nervous system. In this study, we investigated the effect of VIP on IL-12, TNF alpha and nitric oxide (NO) production in macrophages following activation with lipopolysaccharide (LPS) or superantigens. In vitro studies show that at physiologic concentrations, VIP inhibited IL-12 and NO but not TNF alpha production in macrophages which were stimulated with LPS or superantigens. The inhibitory effect of VIP on IL-12 production appeared to be cAMP mediated since other cAMP inducing agents were also potent in inhibiting IL-12 production. Since IL-12 plays a critical role in T cell function, we suggest that naturally occurring neural hormones can regulate the type and direction of the immune response.
 CT Check Tags: Animal; Female; Support, Non-U.S. Gov't
 Cyclic AMP: ME, metabolism
 Forskolin: PD, pharmacology
 Interleukin-12: AI, antagonists & inhibitors
 ***Interleukin-12: BI, biosynthesis**
 Lipopolysaccharides: PD, pharmacology
 Macrophages, Peritoneal: DE, drug effects
 Macrophages, Peritoneal: IM, immunology
 *Macrophages, Peritoneal: ME, metabolism
 Mice
 Mice, Inbred Strains
 Mitogens: PD, pharmacology
 Neuropeptides: PD, pharmacology
 Nitric Oxide: AI, antagonists & inhibitors
 *Nitric Oxide: BI, biosynthesis
 Superantigens: PD, pharmacology
 Thioglycolates: PD, pharmacology
 Tumor Necrosis Factor: BI, biosynthesis
 Vasoactive Intestinal Peptide: IM, immunology
 *Vasoactive Intestinal Peptide: PD, pharmacology
 8-Bromo Cyclic Adenosine Monophosphate: PD, pharmacology

 L12 ANSWER 12 OF 23 MEDLINE
 AN 1998208280 MEDLINE
 DN 98208280
 TI Alteration of the cytokine phenotype in an experimental lung granuloma model by inhibiting nitric oxide.
 AU Hogaboam C M; Chensue S W; Steinhauer M L; Huffnagle G B; Lukacs N W; Strieter R M; Kunkel S L
 CS Department of Pathology, University of Michigan Medical School, Ann Arbor 48109-0602, USA.
 NC 1P50HL56402 (NHLBI)
 HL31963 (NHLBI)
 HL35276 (NHLBI)
 +
 SO JOURNAL OF IMMUNOLOGY, (1997 Dec 1) 159 (11) 5585-93.
 Journal code: IFB. ISSN: 0022-1767.
 CY United States
 DT Journal; Article; (JOURNAL ARTICLE)
 LA English
 FS Abridged Index Medicus Journals; Priority Journals; Cancer Journals
 EM 199806

AB Pulmonary granulomatous inflammation modulated by IFN-gamma and IL-12 is also associated with augmented inducible nitric oxide synthase (NOS II). To address the role of increased nitric oxide synthesis in this model, mice received daily i.p. injections of NG-nitro-L-arginine-methyl ester (L-NAME; 8 mg/kg) during both the 2-wk immunization period with purified protein-derivative (PPD) and the subsequent lung challenge with PPD-coated

Sepharose beads. Other groups of animals received saline, L-NAME or NG-nitro-D-arginine-methyl ester (D-NAME; 8 mg/kg) during the pulmonary embolization period and not the PPD sensitization period. On day 4 post-PPD bead challenge, PCR analysis of the whole lung revealed that NOS II expression appeared to be similar in both of the L-NAME treatment protocols. L-NAME-treated mice in both dosing protocols had lung lesions that were significantly larger than granuloma lesions measured in mice that received saline or D-NAME. The enlarged lesions from L-NAME-treated mice contained markedly greater numbers of neutrophils and eosinophils. Equivalent numbers of PPD-activated dispersed cells from whole lungs of L-NAME-treated mice produced significantly higher levels of IL-4 and

IL-10 and smaller amounts of IL-12 and IFN-gamma compared with similar lung cultures derived from control or D-NAME-treated mice. Levels of C-C chemokines such as monocyte chemoattractant protein-1 (MCP-1), C10, and macrophage inflammatory protein-1alpha (MIP-1alpha) were also significantly elevated in lung cultures from L-NAME-treated mice compared with controls. Thus, nitric oxide regulates the size and cellular composition of the Th1-type lung granuloma, possibly through its effects on the cytokine and chemokine profile associated with this lesion.

CT Check Tags: Animal; Female; Support, U.S. Gov't, P.H.S.

*Cytokines: ME, metabolism
 Eosinophils: IM, immunology
 *Granuloma, Respiratory Tract: IM, immunology
 Interferon Type II: ME, metabolism
 Interleukin-10: ME, metabolism
Interleukin-12: ME, metabolism
 Interleukin-4: ME, metabolism
 Lung: EN, enzymology
 *Lung Diseases: IM, immunology
 Mice
 Mice, Inbred CBA
 Neutrophils: IM, immunology
Nitric Oxide: AI, antagonists & inhibitors
 Nitric Oxide: BI, biosynthesis
 *Nitric Oxide: PH, physiology
 Nitric-Oxide Synthase: ME, metabolism
NG-Nitroarginine Methyl Ester: PD, pharmacology
 *Th1 Cells
 Tuberculin: PD, pharmacology
 Tumor Necrosis Factor: ME, metabolism

L12 ANSWER 13 OF 23 MEDLINE

AN 1998180349 MEDLINE

DN 98180349

TI Suppression of IL-12 production by phosphodiesterase inhibition in murine endotoxemia is IL-10 independent.

AU Hasko G; Szabo C; Nemeth Z H; Salzman A L; Vizi E S

CS Department of Pharmacology, Institute of Experimental Medicine, Hungarian Academy of Sciences, Budapest.

SO EUROPEAN JOURNAL OF IMMUNOLOGY, (1998 Feb) 28 (2) 468-72.
 Journal code: EN5. ISSN: 0014-2980.

CY GERMANY: Germany, Federal Republic of

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals; Cancer Journals

EM 199806

AB Phosphodiesterase (PDE) inhibitors are potent regulators of various
 immune
 processes. Immune cells contain type IV and type III PDE. Here we studied
 in mice the effects of rolipram, a selective PDE IV inhibitor, and
 amrinone, a selective PDE III blocker, on plasma levels of IL-12 (p70),
 IFN-gamma, IL-1, TNF-alpha, and nitric oxide (NO) induced by
 intraperitoneal injection of Escherichia coli lipopolysaccharide (LPS)

(80 mg/kg). Pretreatment of BALB/c mice with both rolipram (1-25 mg/kg) and
 amrinone (10-100 mg/kg) decreased plasma IL-12 levels in a dose-dependent
 manner. Similarly, LPS-elicited plasma IFN-gamma concentrations were
 suppressed by both rolipram and amrinone. However, LPS-induced plasma
 IL-1alpha levels were not affected by either of these compounds. In
 addition, rolipram inhibited IL-12, IFN-gamma, TNF-alpha and
 nitrite/nitrate (breakdown products of NO) production in C57BL/6
 IL-10(+/+) mice as well as in their IL-10-deficient counterparts (C57BL/6
 IL-10(-/-)). Our results suggest that rolipram and amrinone decrease the
 immune activation in endotoxemia through inhibition of the production of
 pro-inflammatory mediators IL-12, IFN-gamma, TNF-alpha and NO. These
 effects are not the consequences of the increase in IL-10 production by
 PDE inhibition.

CT Check Tags: Animal; Male; Support, Non-U.S. Gov't
 Amrinone: AD, administration & dosage
 *Endotoxemia: EN, enzymology
 *Endotoxemia: IM, immunology
 Injections, Intraperitoneal
 Interferon Type II: BI, biosynthesis
 Interferon Type II: BL, blood
 Interleukin-10: BI, biosynthesis
 Interleukin-10: DF, deficiency
 *Interleukin-10: PH, physiology
 *Interleukin-12: AI, antagonists & inhibitors
 *Interleukin-12: BI, biosynthesis
 Interleukin-12: BL, blood
 Lipopolysaccharides: AD, administration & dosage
 Mice
 Mice, Inbred BALB C
 Mice, Inbred C57BL
 Mice, Knockout
 Nitric Oxide: AI, antagonists & inhibitors
 Pyrrolidinones: AD, administration & dosage
 Tumor Necrosis Factor: AI, antagonists & inhibitors
 *3',5'-Cyclic-Nucleotide Phosphodiesterase: AI, antagonists & inhibitors

L12 ANSWER 14 OF 23 MEDLINE

AN 97270463 MEDLINE

DN 97270463

TI Role of interleukin-10 in regulation of T-cell-dependent and
 T-cell-independent mechanisms of resistance to Toxoplasma gondii.

AU Neyer L E; Grunig G; Fort M; Remington J S; Rennick D; Hunter C A

CS Department of Immunology and Infectious Diseases, Research Institute,
Palo Alto Medical Foundation, California 94301, USA.

NC AI35956 (NIAID)

SO INFECTION AND IMMUNITY, (1997 May) 65 (5) 1675-82.
Journal code: GO7. ISSN: 0019-9567.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals; Cancer Journals

EM 199707

EW 19970703

AB Interleukin-10 (IL-10) is a cytokine which can inhibit T-cell and natural killer (NK) cell functions associated with cell-mediated immunity to intracellular infections. The production of IL-10 by mice infected with *Toxoplasma gondii* has been implicated in the suppression of lymphocyte proliferation observed during acute toxoplasmosis, as well as susceptibility to infection with this parasite. We have used C57BL/6 mice which lack a functional IL-10 gene (IL-10(-/-) mice) to investigate the role of IL-10 in acute toxoplasmosis. Intraperitoneal infection of IL-10(-/-) mice with *T. gondii* resulted in 100% mortality by day 13, whereas wild-type C57BL/6 (WT) mice survived acute infection. IL-10(-/-) mice infected with *T. gondii* had significantly higher serum levels of IL-12 and gamma interferon (IFN-gamma) than WT mice. Early mortality of infected IL-10(-/-) mice was prevented by treatment with IL-10 and significantly delayed by neutralizing antibodies to IL-12 and IFN-gamma. Further studies revealed that SCID/IL-10(-/-) mice infected with *T. gondii* had delayed time to death compared to IL-10(-/-) mice, indicating that lymphocytes contributed to death of IL-10(-/-) mice. In addition, infected SCID/IL-10(-/-) mice survived longer than infected SCID mice. These latter data indicate that in mice lacking lymphocytes, endogenous IL-10 is associated with increased susceptibility to *T. gondii*. However, the lack of IL-10 does not alter the infection-induced suppression of T cell and NK cell functions. Our experiments reveal that IL-10 is associated with protection or increased susceptibility to infection with *T. gondii*, depending on whether mice possess lymphocytes, and demonstrate the important roles of IL-12 and IFN-gamma in the early infection-induced mortality observed in the IL-10(-/-) mice.

CT Check Tags: Animal; Female; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.

omega-N-Methylarginine: PD, pharmacology
Antibodies, Blocking: IM, immunology
Cell Division
Enzyme-Linked Immunosorbent Assay
Flow Cytometry
*Immunity, Natural: GE, genetics
Interferon Type II: BL, blood
Interferon Type II: IM, immunology
Interferon Type II: ME, metabolism
*Interleukin-10: GE, genetics
*Interleukin-10: IM, immunology
Interleukin-10: PD, pharmacology
Interleukin-12: BL, blood

Interleukin-12: IM, immunology
 Interleukin-12: ME, metabolism
 Killer Cells, Natural: CY, cytology
 *Killer Cells, Natural: IM, immunology
 Mice
 Mice, Inbred C57BL
 Mice, Mutant Strains
 Mice, SCID
 Neutralization Tests
 Nitrites: ME, metabolism
 T-Lymphocytes: CY, cytology
 *T-Lymphocytes: IM, immunology
 *Toxoplasmosis, Animal: IM, immunology

L12 ANSWER 15 OF 23 MEDLINE
 AN 97258616 MEDLINE
 DN 97258616
 TI Intracellular antimicrobial activity in the absence of interferon-gamma:
 effect of interleukin-12 in experimental visceral leishmaniasis in
 interferon-gamma gene-disrupted mice.
 AU Taylor A P; Murray H W
 CS Department of Medicine, Cornell University Medical College, New York
 10021, USA.
 NC AI-16963 (NIAID)
 SO JOURNAL OF EXPERIMENTAL MEDICINE, (1997 Apr 7) 185 (7) 1231-9.
 Journal code: I2V. ISSN: 0022-1007.
 CY United States
 DT Journal; Article; (JOURNAL ARTICLE)
 LA English
 FS Priority Journals; Cancer Journals
 EM 199707
 EW 19970703
 AB Despite permitting uncontrolled intracellular visceral infection for 8
 wk,
 interferon-gamma (IFN-gamma) gene knockout (GKO) mice infected with
 Leishmania donovani proceeded to reduce liver parasite burdens by 50% by
 week 12. This late-developing IFN-gamma-independent antileishmanial
 mechanism appeared to be dependent largely on endogenous tumor necrosis
 factor-alpha (TNF-alpha): L. donovani infection induced TNF-alpha mRNA
 expression in parasitized GKO livers and neutralization of TNF-alpha
 reversed control at week 12.7 d of treatment of infected GKO mice with
 interleukin-12 (IL-12) readily induced leishmanicidal activity and also
 partially restored the near-absent tissue granulomatous response,
 observations that for the first time expand the antimicrobial repertoire
 of IL-12 to include IFN-gamma-independent effects. The action of IL-12
 against L. donovani was TNF-alpha dependent and required the activity of
 inducible nitric oxide synthase. These results point to the presence of
 an
 IFN-gamma-independent antimicrobial mechanism, mediated by TNF-alpha,
 which remains quiescent until activated late in the course of
 experimental
 visceral leishmaniasis. However, as judged by the effect of exogenous
 IL-12 this quiescent mechanism can readily be induced to rapidly yield
 enhanced intracellular antimicrobial activity.
 CT Check Tags: Animal; Female; Male; Support, U.S. Gov't, P.H.S.
 Drug Interactions
 Enzyme Inhibitors

Gene Expression
 Granuloma: PS, parasitology
 Guanidines: PD, pharmacology
 *Interferon Type II: DF, deficiency
 Interferon Type II: GE, genetics
 *Interleukin-12: PD, pharmacology
 *Leishmaniasis, Visceral: IM, immunology
 Liver: EN, enzymology
 Liver: PS, parasitology
 Mice
 Mice, Inbred C57BL
 Mice, Knockout
Nitric-Oxide Synthase: AI, antagonists & inhibitors
 Nitric-Oxide Synthase: BI, biosynthesis
 Nitric-Oxide Synthase: GE, genetics
 RNA, Messenger: AN, analysis
 Tumor Necrosis Factor: BI, biosynthesis
 Tumor Necrosis Factor: GE, genetics

L12 ANSWER 16 OF 23 MEDLINE
 AN 97176660 MEDLINE
 DN 97176660
 TI Neospora caninum: role for immune cytokines in host immunity.
 AU Khan I A; Schwartzman J D; Fonseka S; Kasper L H
 CS Department of Medicine, Dartmouth Medical School, Hanover, New Hampshire
 03755, USA.
 SO EXPERIMENTAL PARASITOLOGY, (1997 Jan) 85 (1) 24-34.
 Journal code: EQP. ISSN: 0014-4894.
 CY United States
 DT Journal; Article; (JOURNAL ARTICLE)
 LA English
 FS Priority Journals
 EM 199705
 EW 19970501
 AB Neospora caninum is a coccidial protozoan parasite that infects a large
 range of mammals including dogs, cats, mice, and cattle. Morphologically,
 N. caninum appears indistinguishable from Toxoplasma gondii, although
 they are genetically distinct. To date there have been no reported cases of
 this infection in humans, although nonhuman primates may be susceptible
 to infection. Inbred A/J mice develop no clinical and little histologic
 evidence of infection in spite of a high-dose inoculum of N. caninum.
 Splenocytes obtained from infected mice proliferate in vitro in response
 to both N. caninum and T. gondii-soluble antigen. A transient state of T
 cell hyporesponsiveness to parasite antigen and mitogen was observed at
 Day 7 p.i. This downregulatory response could be partially reversed by
 the addition of the nitric oxide antagonist LNMMA, but not antibody to IL-10.
 Mice infected with N. caninum produce significant quantities of IL-12 and
 IFN gamma, most evident shortly after infection. In vivo, antibody to
 IL-12 is able to neutralize immune resistance to the parasite. Moreover,
 in vivo depletion of IFN gamma with antibody renders the mice susceptible
 to infection. These observations suggest that N. caninum induces a T cell
 immune response in the infected host that is at least partially mediated
 by IL-12 and IFN gamma.
 CT Check Tags: Animal; Female; Human

omega-N-Methylarginine: PD, pharmacology
 Brain: PA, pathology
 Brain: PS, parasitology
 *Coccidiosis: IM, immunology
 Cytokines: GE, genetics
 Cytokines: IM, immunology
 *Cytokines: PH, physiology
 Disease Susceptibility
 Down-Regulation (Physiology): DE, drug effects
 Immunity, Cellular
 Interferon Type II: GE, genetics
 Interferon Type II: IM, immunology
 Interferon Type II: PH, physiology
 Interleukin-10: GE, genetics
 Interleukin-10: IM, immunology
 Interleukin-10: PH, physiology
 Interleukin-12: **GE, genetics**
 Interleukin-12: **IM, immunology**
 Interleukin-12: **PH, physiology**
 Interleukin-2: GE, genetics
 Interleukin-2: IM, immunology
 Interleukin-2: PH, physiology
 Liver: PA, pathology
 Liver: PS, parasitology
 Lymphocyte Transformation
 Mice
 *Neospora: IM, immunology
 Nitric Oxide: **AI, antagonists & inhibitors**
 Nitric Oxide: PH, physiology
 Pancreas: PA, pathology
 Pancreas: PS, parasitology
 RNA, Messenger: BI, biosynthesis
 Spleen: CY, cytology
 Spleen: IM, immunology
 Spleen: PS, parasitology
 T-Lymphocytes: IM, immunology

L12 ANSWER 17 OF 23 MEDLINE
 AN 96295525 MEDLINE
 DN 96295525
 TI Interferon-gamma-dependent expression of inducible nitric oxide synthase, interleukin-12, and interferon-gamma-inducing factor in macrophages elicited by allografted tumor cells.
 AU Sanchez-Bueno A; Verkhusha V; Tanaka Y; Takikawa O; Yoshida R
 CS Department of Cell Biology, Osaka Bioscience Institute, Japan.
 SO BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, (1996 Jul 16) 224 (2)
 555-63.
 Journal code: 9Y8. ISSN: 0006-291X.
 CY United States
 DT Journal; Article; (JOURNAL ARTICLE)
 LA English
 FS Priority Journals; Cancer Journals
 EM 199611
 AB We have examined the mechanisms of activation of macrophages (Mos) induced

by i.p. allografted Meth A tumor cells (Meth A-Mos) during the rejection

of the cells by C57BL/6 mice. Inducible nitric oxide (NO) synthase (iNOS), interleukin-12 (IL-12), and interferon-gamma (IFN-gamma)-inducing factor (IGIF) were transiently expressed in Meth A-Mos during the rejection. The expression was impaired in mice in which the gene encoding IFN-gamma had been disrupted (IFN-gamma-/-). In vitro studies showed that Meth A-Mos from IFN-gamma +/+ mice induced an apoptotic type of cell death in P815 cells, without cell-to-cell contact, in an NO-dependent manner, whereas Meth A-Mos from IFN-gamma-/- mice could not lyse these cells. The iNOS, IL-12, and IGIF expression was also impaired in bacteria-activated Mos from IFN-gamma-/-mice, indicating that IFN-gamma, but not IGIF, would be the initial signal that leads to the activation of Mos in vivo.

CT Check Tags: Animal; Male; Support, Non-U.S. Gov't

Apoptosis
 Arginine: AA, analogs & derivatives
 Arginine: PD, pharmacology
 Base Sequence
 Cell Line
 Cell Survival: DE, drug effects
 Cells, Cultured
 *Cytokines: BI, biosynthesis
 DNA: AN, analysis
 DNA Primers
 Enzyme Induction
 Enzyme Inhibitors: PD, pharmacology
 Fibrosarcoma: EN, enzymology
 *Fibrosarcoma: IM, immunology
 Gene Expression
 Interferon Type II: GE, genetics
 *Interferon Type II: PH, physiology
 *Interleukin-12: BI, biosynthesis
 Macrophages: EN, enzymology
 *Macrophages: IM, immunology
 Mice
 Mice, Inbred C57BL
 Mice, Knockout
 Molecular Sequence Data
 Mycobacterium bovis: IM, immunology
 *Neoplasm Transplantation
 Nitric-Oxide Synthase: AI, antagonists & inhibitors
 *Nitric-Oxide Synthase: BI, biosynthesis
 Polymerase Chain Reaction
 Time Factors
 Transplantation, Homologous

L12 ANSWER 18 OF 23 MEDLINE

AN 96280727 MEDLINE

DN 96280727

TI Interleukin-12 gene-expression of macrophages is regulated by nitric oxide.

AU Rothe H; Hartmann B; Geerlings P; Kolb H

CS Diabetes Research Institute, Heinrich- Heine University of Dusseldorf, Germany.

SO BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, (1996 Jul 5) 224 (1) 159-63.

Journal code: 9Y8. ISSN: 0006-291X.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)
 LA English
 FS Priority Journals; Cancer Journals
 EM 199610
 AB Interleukin-12 is a heterodimeric cytokine, mainly produced by macrophages. In our present study we demonstrate that interleukin-12 expression is regulated by nitric oxide. Incubation of the macrophage cell line IC 21 with interferon-gamma gave rise to both interleukin-12 p40 mRNA and nitric oxide production. The concurrent addition of the nitric oxide synthase inhibitor N(G)-monomethyl-L-arginine inhibited nitrite production and in parallel completely suppressed interleukin-12 p40 mRNA formation. This indicated that endogenous nitric oxide synthase activity was required for IL-12 p40 gene expression. Exposure of the cells towards the nitric oxide generating compounds nitroprusside or S-nitroso-N-acetylpenicillamine induced interleukin-12 p40 mRNA. Maximal mRNA levels were induced with nitric oxide donors at 1 micromolar concentration. We conclude that nitric oxide may exert an autoregulatory and paracrine control of interleukin-12 gene expression.

CT Check Tags: Animal; Support, Non-U.S. Gov't
 *Arginine: AA, analogs & derivatives
 Arginine: PD, pharmacology
 Cell Line
 Enzyme Inhibitors: PD, pharmacology
 Gene Expression Regulation: DE, drug effects
 *Gene Expression Regulation: IM, immunology
 Interferon-gamma, Recombinant: PD, pharmacology
 *Interleukin-12: BI, biosynthesis
 Macrophage Activation
 Macrophages: DE, drug effects
 *Macrophages: IM, immunology
 Mice
 *Nitric Oxide: PH, physiology
 Nitric-Oxide Synthase: AI, antagonists & inhibitors
 Nitroprusside: PD, pharmacology
 Penicillamine: AA, analogs & derivatives
 Penicillamine: PD, pharmacology
 Rats
 RNA, Messenger: BI, biosynthesis
 Transcription, Genetic: DE, drug effects

L12 ANSWER 19 OF 23 MEDLINE
 AN 96197369 MEDLINE
 DN 96197369
 TI Effects of N(g)-methyl-L-arginine, an inhibitor of nitric oxide synthesis, on interleukin-2-induced capillary leakage and antitumor responses in healthy and tumor-bearing mice.

AU Orucevic A; Lala P K
 CS Department of Anatomy, University of Western Ontario, Canada.
 SO CANCER IMMUNOLOGY, IMMUNOTHERAPY, (1996 Jan) 42 (1) 38-46.
 Journal code: CN3. ISSN: 0340-7004.
 CY GERMANY: Germany, Federal Republic of
 DT Journal; Article; (JOURNAL ARTICLE)

LA English
 FS Priority Journals; Cancer Journals
 EM 199608
 AB We tested whether treatment with an inhibitor of nitric oxide synthesis (N{g}-methyl-L-arginine, MeArg) can ameliorate interleukin-2(IL-2)-therapy-induced capillary leak syndrome in healthy or tumor-bearing mice without compromising the antitumor effects of IL-2 therapy. Healthy or C3-L5-mammary-adenocarcinoma-bearing C3H/HeJ mice were treated with one or two rounds of various doses of IL-2 (ten injections, i. p., every 8 h) or MeArg (ten injections s. c., every 8 h) or their combination. In an additional experiment, MeArg was given chronically in the drinking water, rather than s. c. to healthy mice subjected to one round of therapy as above. Mice were killed 1 h after their last IL-2 injection to measure the water content of the lungs and pleural cavities (markers of capillary leakage), NO production (given by NO₂- and NO₃- levels in the serum and pleural effusion), as well as the effect of therapies on the primary tumor size and number of spontaneous lung metastatic nodules. Results revealed that all doses of IL-2 (7500-35000 Cetus U/injection), as well as both rounds of IL-2 therapy, caused capillary leakage. However, no pleural effusion was seen after the second round in any of the IL-2-treated groups. MeArg therapy, given subcutaneously (5-20 mgkg⁻¹ injection(-1) in healthy and 20 mgkg⁻¹ injection(-1) in tumor-bearing mice), did not ameliorate IL-2-induced capillary leakage in either group of mice, and did not compromise antitumor effects of IL-2. However, subcutaneous MeArg therapy alone reduced the growth of the primary tumors, the occurrence of lung metastases and the amount of tumor-induced pulmonary edema. When MeArg therapy was given orally (1 mg/ml drinking water), a substantial drop in NO production, as well as reduction in capillary leakage was noted in IL-2-treated healthy mice. These findings suggest that NO inhibitors could be a valuable adjunct to IL-2 therapy of cancer and infectious diseases.

CT Check Tags: Animal; Female; Support, Non-U.S. Gov't
 *Adenocarcinoma: DT, drug therapy
 Adenocarcinoma: ME, metabolism
 Antineoplastic Agents: PD, pharmacology
 Antineoplastic Agents: PK, pharmacokinetics
 *Antineoplastic Agents: TO, toxicity
 *Arginine: AA, analogs & derivatives
 Arginine: PD, pharmacology
 *Capillary Permeability: DE, drug effects
 Cell Division: DE, drug effects
 Dose-Response Relationship, Drug
 Drug Interactions
 *Enzyme Inhibitors: PD, pharmacology
 Interleukin-12: PD, pharmacology
 *Interleukin-12: TO, toxicity
 *Mammary Neoplasms, Experimental: DT, drug therapy
 Mammary Neoplasms, Experimental: ME, metabolism
 Mice
 Mice, Inbred C3H
 Nitric Oxide: AI, antagonists & inhibitors

*Nitric Oxide: BI, biosynthesis
Nitric-Oxide Synthase: AI, antagonists & inhibitors
 Pleural Effusion: CI, chemically induced
 Pulmonary Edema: CI, chemically induced

L12 ANSWER 20 OF 23 MEDLINE
 AN 96180196 MEDLINE
 DN 96180196
 TI Bacterial superantigen-induced human lymphocyte responses are nitric oxide dependent and mediated by IL-12 and IFN-gamma.
 AU Sriskandan S; Evans T J; Cohen J
 CS Department of Infectious Diseases and Bacteriology, Royal Postgraduate Medical School, Hammersmith Hospital, London, United Kingdom.
 SO JOURNAL OF IMMUNOLOGY, (1996 Apr 1) 156 (7) 2430-5.
 Journal code: IFB. ISSN: 0022-1767.
 CY United States
 DT Journal; Article; (JOURNAL ARTICLE)
 LA English
 FS Abridged Index Medicus Journals; Priority Journals; Cancer Journals
 EM 199611
 AB Bacterial superantigens cause marked proliferation of T cells and release of lymphokines. Nitric oxide, derived from the conversion of L-arginine to L-citrulline, inhibits this activation in murine cells. We have now investigated the roles of IL-12, IFN-gamma, lymphotoxin-alpha, and nitric oxide during superantigen-induced human lymphocyte activation. Lymphocyte activation was determined by measurement of proliferative responses and lymphokine release. Both toxic shock syndrome toxin-1 from Staphylococcus aureus and recombinant streptococcal pyrogenic exotoxin A induced proliferation and production of IFN-gamma, lymphotoxin-alpha, and IL-12 by human mononuclear cells in a time-dependent fashion. The release of IFN-gamma was abrogated by a neutralizing Ab to IL-12, but lymphocyte proliferative responses were unaffected. A neutralizing Ab to IFN-gamma prevented the release of lymphotoxin-alpha, but did not affect proliferation. The neutralization of lymphotoxin-alpha using two different Abs did not affect IFN-gamma release or proliferation. In contrast to previous findings in mice, the arginine analogue, NG-monomethyl-L-arginine, significantly inhibited both proliferation and lymphokine release by superantigen-stimulated human cells. Thus, the release of lymphotoxin-alpha by lymphocytes following superantigen stimulation is dependent upon the presence of IFN-gamma; the IFN-gamma response is in turn under the control of IL-12. There is no evidence that nitric oxide plays an inhibitory role during superantigen-mediated human lymphocyte activation. Indeed, arginine is a prerequisite for such activation.
 CT Check Tags: Animal; Human; In Vitro
 Antibodies, Monoclonal: PD, pharmacology
 Arginine: AA, analogs & derivatives
 Arginine: PD, pharmacology
 Base Sequence
 DNA Primers: GE, genetics
 Enzyme Inhibitors: PD, pharmacology
 Exotoxins: AD, administration & dosage
 Exotoxins: GE, genetics
 Interferon Type II: AI, antagonists & inhibitors

*Interferon Type II: BI, biosynthesis
 Interleukin-12: AI, antagonists & inhibitors
 *Interleukin-12: BI, biosynthesis
 Kinetics
 Lymphocyte Transformation: DE, drug effects
 *Lymphocyte Transformation: PH, physiology
 Lymphocytes: DE, drug effects
 Lymphocytes: IM, immunology
 Lymphocytes: ME, metabolism
 Lymphotoxin: AI, antagonists & inhibitors
 Lymphotoxin: BI, biosynthesis
 Mice
 Molecular Sequence Data
 Neutralization Tests
 *Nitric Oxide: ME, metabolism
 Nitric-Oxide Synthase: AI, antagonists & inhibitors
 Nitrites: ME, metabolism
 *Superantigens: AD, administration & dosage
 Superantigens: GE, genetics

L12 ANSWER 21 OF 23 MEDLINE

AN 96132990 MEDLINE

DN 96132990

TI Production of nitric oxide (NO) is not essential for protection against acute Toxoplasma gondii infection in IRF-1-/- mice.

AU Khan I A; Matsuura T; Fonseka S; Kasper L H

CS Department of Medicine, Dartmouth Medical School, Hanover, NH 03755, USA.

NC AI19613 (NIAID)

AI35956 (NIAID)

AI33325 (NIAID)

SO JOURNAL OF IMMUNOLOGY, (1996 Jan 15) 156 (2) 636-43.

Journal code: IFB. ISSN: 0022-1767.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Abridged Index Medicus Journals; Priority Journals; Cancer Journals

EM 199604

AB Production of nitric oxide (NO) by macrophages is important for the killing of intracellular pathogens. IFN-gamma and LPS stimulate NO production by transcriptional up-regulation of inducible nitric oxide synthetase (iNOS). In the present study we used mice with a targeted disruption of the IFN regulatory factor-1 gene (IRF-1-/-) to investigate the importance of NO in the host immune response against Toxoplasma gondii, a major cause of infection in newborns and those with AIDS. IRF-1-/- mice were more susceptible to acute Toxoplasma infection, and treatment with either exogenous IFN-gamma or in vivo neutralization of endogenous IFN-gamma had little effect on their susceptibility to infection. However, administration of exogenous IL-12 was able to prolong survival even when IFN-gamma was depleted. An in vivo depletion study suggested that the mechanism of this protective response is mediated in part by CD4+ T cells. The administration of IL-12 could not overcome the inhibition of lymphoproliferative response in T. gondii-infected mice and treatment with N-monomethyl-L-arginine (L-NMMA), a nitric oxide synthase (iNOS) antagonist in vitro was unable to reverse the immunosuppression.

In

response to Toxoplasma infection, splenocytes from IRF-1-/- mice exhibited

increased production of IL-10 as well as a 30-fold increase in its message

expression. These studies indicate that NO may not be essential for host immunity to the parasite, and moreover that IL-12 appears to induce an IFN-gamma-independent mechanism of protection against this opportunistic pathogen.

CT Check Tags: Animal; Female; Support, U.S. Gov't, P.H.S.

Arginine: AA, analogs & derivatives

Arginine: PD, pharmacology

Biological Response Modifiers: TU, therapeutic use

CD4-Positive T-Lymphocytes

Disease Susceptibility: GE, genetics

DNA-Binding Proteins: GE, genetics

*DNA-Binding Proteins: PH, physiology

Interferon Type II: PD, pharmacology

Interleukin-10: PD, pharmacology

Interleukin-12: PD, pharmacology

***Interleukin-12: TU, therapeutic use**

Lymphocyte Depletion

Lymphocyte Transformation

Mice

Mice, Inbred C57BL

Mice, Knockout

*Nitric Oxide: PH, physiology

Nitric-Oxide Synthase: AI, antagonists & inhibitors

Phosphoproteins: GE, genetics

*Phosphoproteins: PH, physiology

T-Lymphocyte Subsets: DE, drug effects

*T-Lymphocyte Subsets: IM, immunology

*Toxoplasma: PH, physiology

*Toxoplasmosis, Animal: PC, prevention & control

Toxoplasmosis, Animal: TH, therapy

Transforming Growth Factor beta: PD, pharmacology

L12 ANSWER 22 OF 23 MEDLINE

AN 95332736 MEDLINE

DN 95332736

TI IL-12 prevents mortality in mice infected with *Histoplasma capsulatum* through induction of IFN-gamma.

AU Zhou P; Sieve M C; Bennett J; Kwon-Chung K J; Tewari R P; Gazzinelli R T; Sher A; Seder R A

CS Lymphokine Regulation Unit, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD 20892, USA..

SO JOURNAL OF IMMUNOLOGY, (1995 Jul 15) 155 (2) 785-95.

Journal code: IFB. ISSN: 0022-1767.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Abridged Index Medicus Journals; Priority Journals; Cancer Journals

EM 199510

AB *Histoplasma capsulatum* is a pathogenic fungus found in discrete geographic

locations throughout the world. The fungus invades the reticuloendothelial

organs such as the spleen and liver of immunocompetent hosts where it is usually controlled. However, in individuals with immune deficiency, histoplasmosis is a severe and potentially fatal disease. Resistance to

this infection is due primarily to a cellular immune response mediated by T cells and macrophages. Moreover, IFN-gamma is critical in activating macrophages to kill the organism. Herein we study the regulation of cytokine induction in mice infected with *H. capsulatum* and the effects of IL-12 in the course of infection. Mice infected with *H. capsulatum* and treated with neutralizing Abs to IFN-gamma, TNF-alpha, or IL-12 experienced accelerated mortality, indicating that endogenous production of these cytokines plays an important role in response to infection. In contrast, mice treated with IL-12 or a neutralizing Ab to IL-4 at the initiation of infection had substantially diminished mortality. Moreover, mice infected and treated with IL-12 show a two- to threefold increase in the amount of IFN-gamma following in vitro stimulation with specific *H. capsulatum* Ag compared with the control infected mice. The protective effect of IL-12 could be abrogated if a neutralizing Ab to IFN-gamma was given at the same time, demonstrating that the role of IL-12 in protection was mediated by IFN-gamma. Additionally, infected mice treated with IL-12 had a severalfold decrease in the colony counts of *H. capsulatum* in spleen cells after 5 days of infection as compared with control animals. Lastly, spleen cells from infected animals treated with IL-12 showed a striking decrease in their proliferative response to mitogen or *H. capsulatum* Ag. Responses could be restored by adding inhibitors of IFN-gamma or of nitric oxide to the in vitro cultures. The above observations suggest that IL-12 may be useful in immunologic intervention against this opportunistic pathogen.

CT Check Tags: Animal; Female
 Antibodies: IM, immunology
 Antibody Formation
 Antigens, Fungal: PD, pharmacology
 Binding, Competitive: IM, immunology
 Cell Division: IM, immunology
 Histoplasmosis: IM, immunology
 *Histoplasmosis: MO, mortality
 *Histoplasmosis: TH, therapy
 Immunity, Cellular
 Interferon Type II: AI, antagonists & inhibitors
 *Interferon Type II: BI, biosynthesis
 Interferon Type II: PH, physiology
 Interleukin-12: GE, genetics
 *Interleukin-12: PH, physiology
 *Interleukin-12: TU, therapeutic use
 Interleukin-4: BI, biosynthesis
 Lymphocyte Transformation: IM, immunology
 Mice
 Mice, Inbred C57BL
 Mitogens: PD, pharmacology
 Nitric Oxide: AI, antagonists & inhibitors
 RNA, Messenger: BI, biosynthesis
 Spleen: CY, cytology
 Tumor Necrosis Factor: AI, antagonists & inhibitors
 Tumor Necrosis Factor: BI, biosynthesis
 Tumor Necrosis Factor: PH, physiology

L12 ANSWER 23 OF 23 MEDLINE
 AN 95024182 MEDLINE

DN 95024182
 TI Interleukin 12 induction of interferon gamma-dependent protection against malaria.
 AU Sedegah M; Finkelman F; Hoffman S L
 CS Malaria Program, Naval Medical Research Institute, Bethesda, MD 20889-5607.
 SO PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1994 Oct 25) 91 (22) 10700-2.
 Journal code: PV3. ISSN: 0027-8424.
 CY United States
 DT Journal; Article; (JOURNAL ARTICLE)
 LA English
 FS Priority Journals; Cancer Journals
 EM 199501
 AB Intraperitoneal injection of recombinant Interleukin 12 (rIL-12) at 30 ng/day for 5 days beginning 1 to 2 days before sporozoite challenge or administration of a single dose of 150 ng of rIL-122 days before challenge
 in protected 100% of BALB/c mice against challenge with 10(2) Plasmodium yoelii sporozoites. rIL-12-induced protection was eliminated in all mice by administration of a monoclonal antibody against interferon gamma and
 50% of mice by administration of NG-monomethyl-L-arginine, a competitive inhibitor of nitric oxide synthase. rIL-12 protected BALB/c mice treated with cytotoxic anti-CD4 and anti-CD8 monoclonal antibodies, as well as T-cell- and B-cell-deficient severe combined immunodeficiency mice. These data suggest that rIL-12 stimulates non-B, non-T cells to produce interferon gamma that kills intrahepatic parasites by stimulating nitric oxide production. If rIL-12 proves to be well tolerated by humans, our findings support consideration of rIL-12 as an immunoprophylactic against malaria.
 CT Check Tags: Animal; Female; Support, U.S. Gov't, Non-P.H.S.
 Antibodies, Monoclonal
 Arginine: AA, analogs & derivatives
 Arginine: PD, pharmacology
 *B-Lymphocytes: IM, immunology
 CD4-Positive T-Lymphocytes: IM, immunology
 CD8-Positive T-Lymphocytes: IM, immunology
 Interferon Type II: IM, immunology
 *Interferon Type II: PH, physiology
 *Interleukin-12: PD, pharmacology
 Killer Cells, Natural: IM, immunology
 Lymphocyte Depletion
 *Malaria: IM, immunology
 Malaria: PC, prevention & control
 Mice
 Mice, Inbred BALB C
 Mice, SCID
 Nitric Oxide: AI, antagonists & inhibitors
 Nitric Oxide: BI, biosynthesis
 *Plasmodium yoelii
 Rats
 Recombinant Proteins: PD, pharmacology
 *T-Lymphocytes: IM, immunology

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L1 4244 S INTERLEUKIN 12/CT
L2 2057 S L1/MAJ
L3 28006 S NITRIC OXIDE/CT
L4 3789 S NITRIC OXIDE SYNTHASE INHIBITOR/CT
L5 12926 S NITRIC OXIDE SYNTHASE/CT
L6 55 S L2 AND L3
L7 3 S L4 AND L2
L8 38 S L5 AND L2
L9 80 S L8 OR L6
L10 789071 S INHIBIT?
L11 184152 S ANTAGONIS?
L12 892752 S L11 OR L10
L13 34 S L12 AND L9
E IMMUNOSTIMULANTS/CT
E E5+ALL
E IMMUNOSTIUMLANTS/CT
E E1+ALL
L14 7786 S IMMUNOSTIMULATION/CT
L15 4 S L14 AND L9
E ADJUVANTS/CT
E E5+ALL
E IMMUNOLOGICAL ADJUVANT/CT
E E3+ALL
L16 1181 S IMMUNOLOGICAL ADJUVANT/CT
L17 0 S L9 AND L16
L18 89833 S VACCIN?
L19 6 S L9 AND L18
L20 0 S L9 AND SCAVENG?
L21 13 S L19 OR L15 OR L7
L22 27 S L13 NOT L21

FILE 'EMBASE' ENTERED AT 11:38:48 ON 22 FEB 2001

=> d bib ab ct l21 1-13;d bib ab ct l22 1-27

L21 ANSWER 1 OF 13 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN 2000233239 EMBASE
TI Interleukin-12 (IL-12) enhancement of the cellular immune response
against

human immunodeficiency virus type 1 Env antigen in a DNA prime/
vaccinia virus boost **vaccine** regimen is time and dose
dependent: Suppressive effects of IL-12 boost are mediated by nitric
oxide.

AU Gherardi M.M.; Ramirez J.C.; Esteban M.

CS M. Esteban, Centro Nacional Biotecnologia, (CSIC), Campus Cantoblanco,
28049 Madrid, Spain. mesteban@cnb.uam.es

SO Journal of Virology, (2000) 74/14 (6278-6286).

Refs: 59

ISSN: 0022-538X CODEN: JOVIAM

CY United States

DT Journal; Article

FS 004 Microbiology

026 Immunology, Serology and Transplantation

LA English

SL English

AB We previously demonstrated that codelivery of interleukin-12 (IL-12) with
the human immunodeficiency virus type 1 (HIV-1) Env antigen from a
recombinant **vaccinia** virus (rVV) can enhance the specific
anti-Env cell-mediated immune (CMI) response. In the present study, we
have investigated the effects of IL-12 in mice when it is expressed in a
DNA prime/VV boost **vaccine** regimen. The delivery of IL-12 and
Env product during priming with a DNA vector, followed by a booster with
VV expressing the Env gene (rVVenv), was found to trigger the optimal CMI
response compared with other immunization schedules studied.
Significantly, if IL-12 is also delivered as a booster from the viral
vector, an impairment of the effects of IL-12 was observed involving
nitric oxide (NO), since it was overcome by specific inhibitors of
inducible NO synthase. NO caused transient immunosuppression rather than
impairment of viral replication. Moreover, at certain viral doses,
coadministration of the NO inhibitor during the booster resulted in
IL-12-mediated enhancement of the specific CD8+ T-cell response. In
addition, the dose of the IL-12-encoding plasmid (pIL-12) and the route

of

administration of both vectors were relevant factors for optimal CMI
responses. Maximal numbers of Env-specific CD8+ gamma

interferon-secreting

cells were obtained when 50 .mu.g of pIL-12 was administered
intramuscularly at priming, followed by an intravenous rVVenv boost. Our
results demonstrate, in a murine model, critical parameters affecting the
success of **vaccination** schedules based on a combination of DNA
and VV vectors in conjunction with immunomodulators.

CT Medical Descriptors:

*cellular immunity

*Human immunodeficiency virus 1

*immune response

Vaccinia virus

virus recombinant

envelope gene

virus replication

cytokine release

immunization

virus vector

dose response

immunomodulation

human

nonhuman

mouse
 animal experiment
 human cell
 animal cell
 article
 priority journal
 Drug Descriptors:
 *interleukin 12
 *virus antigen: EC, endogenous compound
 *virus envelope protein: EC, endogenous compound
 *nitric oxide
 *nitric oxide synthase
 *virus DNA: EC, endogenous compound

L21 ANSWER 2 OF 13 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
 AN 2000009208 EMBASE
 TI IL-4 and IL-10 antagonize IL-12-mediated protection against acute
vaccinia virus infection with a limited role of IFN-.gamma. and
 nitric oxide synthetase 2.
 AU Van den Broek M.; Bachmann M.F.; Kohler G.; Barner M.; Escher R.;
 Zinkernagel R.; Kopf M.
 CS Dr. M. Kopf, Basel Institute for Immunology, Grenzacherstr. 487, 4005
 Basel, Switzerland. kopf@bii.ch
 SO Journal of Immunology, (1 Jan 2000) 164/1 (371-378).
 Refs: 89
 ISSN: 0022-1767 CODEN: JOIMA3
 CY United States
 DT Journal; Article
 FS 004 Microbiology
 026 Immunology, Serology and Transplantation
 LA English
 SL English
 AB Resistance or susceptibility to most infectious diseases is strongly
 determined by the balance of type 1 vs type 2 cytokines produced during
 infection. However, for viruses, this scheme may be applicable only to
 infections with some cytopathic viruses, where IFN-.gamma. is considered
 as mandatory for host defense with little if any participation of type 2
 responses. We studied the role of signature Th1 (IL-12, IFN-.gamma.) and
 Th2 (IL- 4, IL-10) cytokines for immune responses against **vaccinia**
 virus (VV). IL-12(- /-) mice were far more susceptible than
 IFN-.gamma.(-/-) mice, and primary CTL responses against VV were absent
 in
 IL-12(-/-) mice but remained intact in IFN-.gamma.(-/-) mice! Both CD4+
 and CD8+ T cells from IL-12(-/-) mice were unimpaired in IFN-.gamma.
 production, although CD4+ T cells showed elevated Th2 cytokine responses.
 Virus replication was impaired in IL-4(-/-) mice and, even more
 strikingly, in IL-10(-/-) mice, which both produced elevated levels of
 the
 proinflammatory cytokines IL-1.alpha. and IL-6. Thus, IL-4 produced by
 Th2
 cells and IL-10 produced by Th2 cells and probably also by macrophages
 counteract efficient anti-viral host defense. Surprisingly, NO
 production,
 which is considered as a major type 1 effector pathway inhibited by type
 2
 cytokines, appears to play a limited role against VV, because NO
 sythetase

2- deficient mice did not show increased viral replication. Thus, our results identify a new role for IL-12 in defense beyond the induction of IFN-.gamma. and show that IL-4 and IL-10 modulate host protective responses to VV.

CT Medical Descriptors:

***vaccinia**
 *immune response
 host resistance
 infection sensitivity
 cytokine production
 T lymphocyte
 virus replication
 host susceptibility
 immunoregulation
 regulatory mechanism
 nonhuman
 mouse
 animal experiment
 animal model
 animal cell
 article
 priority journal
 Drug Descriptors:
 *interleukin 10: EC, endogenous compound
 *interleukin 4: EC, endogenous compound
***interleukin 12: EC, endogenous compound**
 *gamma interferon: EC, endogenous compound
***nitric oxide synthase**
 interleukin 1: EC, endogenous compound
 interleukin 6: EC, endogenous compound
nitric oxide

L21 ANSWER 3 OF 13 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
 AN 1999389037 EMBASE
 TI Vasoactive intestinal peptide and pituitary adenylate cyclase-activating polypeptide inhibit interleukin-12 transcription by regulating nuclear factor .kappa.B and Ets activation.
 AU Delgado M.; Ganea D.
 CS D. Ganea, Rutgers Univ., Dept. Biological Sciences, 101 Warren St., Newark, NJ 07102, United States. dganea@andromeda.rutgers.edu
 SO Journal of Biological Chemistry, (5 Nov 1999) 274/45 (31930-31940).
 Refs: 70
 ISSN: 0021-9258 CODEN: JBCHA3
 CY United States
 DT Journal; Article
 FS 026 Immunology, Serology and Transplantation
 029 Clinical Biochemistry
 LA English
 SL English
 AB The vasoactive intestinal peptide (VIP) and the structurally related neuropeptide pituitary adenylate cyclase-activating polypeptide (PACAP) act as 'macrophage-deactivating factors'. We showed previously that VIP and PACAP inhibit the production of macrophage-derived tumor necrosis factor-.alpha., interleukin (IL)-6, nitric oxide, and IL-12. This study examines the molecular mechanisms involved in the VIP/PACAP inhibition of IL-12 production. VIP and PACAP inhibit IL-12 (p40) gene expression by affecting both NF-.kappa.B binding and the composition of the Ets-2

binding complex. Both neuropeptides prevent the activation-induced nuclear translocation of the NF- κ B components p65 and c-Rel by inhibiting the reduction in cytoplasmic I κ B α . Moreover, VIP and PACAP inhibit the synthesis of the interferon responsive factor-1. The decrease in nuclear interferon responsive factor-1 and c-Rel results in alterations

of the Ets-2-binding complex. Two transduction pathways, a cAMP-dependent and a cAMP-independent pathway, are involved in the inhibition of IL-12 gene expression and appear to differentially regulate the transcriptional factors involved. Because IL-12 participates in T cell activation and cytolytic T lymphocyte activity and promotes the differentiation of T helper cells into the Th1 subset, the understanding of the mechanisms that

affect IL-12 production in normal and pathological conditions could contribute to immune response-based therapies or vaccine designs.

CT Medical Descriptors:

*transcription regulation
regulatory mechanism
cytokine production
molecular dynamics
gene expression
t lymphocyte activation
immune response
nonhuman

mouse

controlled study

animal cell

article

priority journal

Drug Descriptors:

*vasoactive intestinal polypeptide

*hypophysis adenylate cyclase activating polypeptide

***interleukin 12: EC, endogenous compound**

*immunoglobulin enhancer binding protein: EC, endogenous compound

*neuropeptide

synaptotagmin: EC, endogenous compound

tumor necrosis factor alpha: EC, endogenous compound

nitric oxide: EC, endogenous compound

L21 ANSWER 4 OF 13 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.

AN 1999231229 EMBASE

TI Immune-stimulating complexes induce an IL-12-dependent cascade of innate immune responses.

AU Smith R.E.; Donachie A.M.; Grdic D.; Lycke N.; Mowat A.McI.

CS Dr. A.McI. Mowat, Department of Immunology, University of Glasgow, Western

Infirmery, Glasgow G11 6NT, United Kingdom. a.m.mowat@clinmed.gla.ac.uk

SO Journal of Immunology, (1 May 1999) 162/9 (5536-5546).

Refs: 46

ISSN: 0022-1767 CODEN: JOIMA3

CY United States

DT Journal; Article

FS 026 Immunology, Serology and Transplantation

LA English

SL English

AB The development of subunit **vaccines** requires the use of adjuvants that act by stimulating components of the innate immune response. Immune- stimulating complexes (ISCOMS) containing the saponin adjuvant Quil A are potential **vaccine** vectors that induce a wide range of Ag-specific responses in vivo encompassing both humoral and CD4 and CD8 cell-mediated immune responses. ISCOMS are active by both parenteral and mucosal routes, but the basis for their adjuvant properties is unknown. Here we have investigated the ability of ISCOMS to recruit and activate innate immune responses as measured in peritoneal exudate cells. The i.p. injection of ISCOMS induced intense local inflammation, with early recruitment of neutrophils and mast cells followed by macrophages, dendritic cells, and lymphocytes. Many of the recruited cells had phenotypic evidence of activation and secreted a number of inflammatory mediators, including nitric oxide, reactive oxygen intermediates, IL-1, IL-6, IL-12, and IFN-.gamma.. Of the factors that we investigated further only IL-12 appeared to be essential for the immunogenicity of ISCOMS, as IL-6- and inducible nitric oxide synthase knockout (KO) mice developed normal immune responses to OVA in ISCOMS, whereas these responses were markedly reduced in IL-12KO mice. The recruitment of peritoneal exudate cells following an injection of ISCOMS was impaired in IL-12KO mice, indicating a role for IL-12 in establishing the proinflammatory cascade. Thus, ISCOMS prime Ag-specific immune responses at least in part by activating IL-12-dependent aspects of the innate immune system.

CT Medical Descriptors:
 *inflammation
 *immune response
 antigen specificity
 cellular immunity
 neutrophil
 mast cell
 immunogenicity
 knockout mouse
 immunohistochemistry
 flow cytometry
 phenotype
 nonhuman
 female
 mouse
 animal experiment
 animal model
 controlled study
 animal cell
 article
 priority journal
 Drug Descriptors:
 *interleukin 12
 *iscom
 quil a
 cd4 antigen
 cd8 antigen
 nitric oxide
 interleukin 1
 interleukin 6
 gamma interferon
 nitric oxide synthase

L21 ANSWER 5 OF 13 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.

AN 1999112591 EMBASE

TI Strategies of protection from nitric oxide toxicity in islet inflammation.

AU Rothe H.; Kolb H.

CS H. Rothe, Diabetes Research Institute, Heinrich-Heine Univ. of Dusseldorf,

Auf'm Hennekamp 65, D-40225 Dusseldorf, Germany

SO Journal of Molecular Medicine, (1999) 77/1 (40-44).

Refs: 51

ISSN: 0946-2716 CODEN: JMLME8

CY Germany

DT Journal; Conference Article

FS 003 Endocrinology

005 General Pathology and Pathological Anatomy

LA English

SL English

AB Nitric oxide is thought to contribute to beta cell destruction during islet inflammation in animal models of type I diabetes. In vitro, inhibition of inducible nitric oxide synthase protects islet cells from the damaging effects of inflammatory cells or cytokines. However, the administration of several inducible nitric oxide synthase inhibitors to prediabetic animals had variable effects on disease progression. An alternative approach is to prevent the lethal consequences of nitric oxide

action at the level of islet cells. We observed that the suppression of poly-(ADP-ribose)-polymerase ensures survival of islet cells exposed to nitric oxide. Cells could also be rendered resistant by the induction of endogenous stress proteins in particular of heat shock protein 70. Nitric oxide is not only a strong cytotoxic agent, but is also able to modulate immune reactions by interfering with Th1/Th2 reactivities. This may occur via induction of the interleukin-12 antagonist IL-12(p40)2. Development of type I diabetes is known to be correlated with a shift from a Th2 status during benign insulinitis to a Th1 status during destructive insulinitis. This shift was found dependent on local interleukin-12 gene expression. Indeed, administration of a natural interleukin-12 antagonist suppressed the progression of islet inflammation and concomitant upregulation of the inducible nitric oxide synthase.

CT Medical Descriptors:

*insulin dependent diabetes mellitus

inflammation

pancreas islet beta cell

inflammatory cell

enzyme repression

cell survival

insulinitis

gene expression

helper cell

conference paper

Drug Descriptors:

*nitric oxide

*nitric oxide synthase

*nitric oxide synthase inhibitor

*interleukin 12

cytokine

nicotinamide adenine dinucleotide adenosine diphosphate

ribosyltransferase

heat shock protein 70

L21 ANSWER 6 OF 13 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
 AN 97372660 EMBASE
 DN 1997372660
 TI Interleukin-12 is critical for induction of nitric oxide-mediated immunosuppression following **vaccination** of mice with attenuated *Salmonella typhimurium*.
 AU Schwacha M.G.; Eisenstein T.K.
 CS T.K. Eisenstein, Dept. of Microbiology/Immunology, Temple University School of Medicine, 3400 North Broad St., Philadelphia, PA 19140, United States. tke@astro.ocis.temple.edu
 SO Infection and Immunity, (1997) 65/12 (4897-4903).
 Refs: 75
 ISSN: 0019-9567 CODEN: INFIBR
 CY United States
 DT Journal; Article
 FS 004 Microbiology
 026 Immunology, Serology and Transplantation
 LA English
 SL English
 AB Studies from our laboratory have shown that infection of mice with an attenuated strain of *Salmonella typhimurium* causes a marked suppression in the capacity of splenocytes to generate an in vitro plaque-forming cell (PFC) response to sheep erythrocytes. The suppression has been shown to be mediated by mature, adherent macrophages (M.PHI.s) and nonadherent, precursor M.PHI.s. Nitric oxide has been identified as the suppressor factor. The present study investigated the role of interleukin-12 (IL-12) in the generation of nitric oxide-mediated immunosuppression in this model. *Salmonella* inoculation resulted in marked suppression of PFC responses and high levels of nitrite production. When mice were treated with anti-IL-12 prior to inoculation, nitrite levels in splenocyte cultures were reduced by 75% and the suppression of PFC responses was prevented. The nonadherent splenocyte fraction from *Salmonella*-inoculated mice, which contains precursor M.PHI.s and is weakly immunosuppressive, was treated with IL-12 in vitro. IL-12 augmented the capacity of this fraction to suppress PFC responses by normal splenocytes in a coculture system. Additionally, IL-12 induced nitrite and gamma interferon (IFN-.gamma.) production in a dose-dependent manner. Treatment with anti-IFN-.gamma. blocked nitrite production and suppression, indicating that IFN-.gamma. is an important intermediary in the pathway of IL-12-induced immunosuppression. These results indicate that IL-12 is critical for the induction of nitric oxide-mediated immunosuppression following *S. typhimurium* inoculation and, through its ability to stimulate IFN-.gamma. production, can induce nitric oxide- producing suppressor M.PHI.s.
 CT Medical Descriptors:
 *immunosuppressive treatment
 *salmonella typhimurium
 ***vaccination**
 animal experiment
 article
 controlled study
 erythrocyte

immunomodulation
 inoculation
 macrophage function
 mouse
 nonhuman
 priority journal
 spleen cell
 Drug Descriptors:
 *interleukin 12
 nitric oxide

L21 ANSWER 7 OF 13 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
 AN 97102136 EMBASE
 DN 1997102136
 TI Interleukin-12 synthesis is a required step in trehalose dimycolate-induced activation of mouse peritoneal macrophages.
 AU Oswald I.P.; Dozois C.M.; Petit J.-F.; Lemaire G.
 CS G. Lemaire, URA CNRS 1116, Universite Paris Sud, Batiment 430, 91405 Orsay Cedex, France
 SO Infection and Immunity, (1997) 65/4 (1364-1369).
 Refs: 63
 ISSN: 0019-9567 CODEN: INFIBR
 CY United States
 DT Journal; Article
 FS 004 Microbiology
 026 Immunology, Serology and Transplantation
 LA English
 SL English
 AB Trehalose dimycolate (TDM), a glycolipid present in the cell wall of Mycobacterium spp., is a powerful immunostimulant. TDM primes murine macrophages (M.phi.) to produce nitric oxide (NO) and to develop antitumoral activity upon activation with low doses of lipopolysaccharide (LPS). In this study, we investigated the ability of TDM to induce interleukin 12 (IL-12) and the role of this cytokine in TDM-induced activation of murine M.phi.. RNA isolated from peritoneal exudate cells (PEC) collected at different times after TDM injection was used to determine IL-12 (p35 and p40 subunits) and gamma interferon (IFN-.gamma.) mRNA levels by semiquantitative reverse transcriptase-PCR. Constitutive expression of IL-12p35 was observed in PEC from untreated as well as from TDM-injected mice. In contrast, expression of the IL-12p40 subunit was almost undetectable in control PEC but was dramatically upregulated in PEC from TDM-injected mice. IL-12p40 expression peaked at 8 h and subsided to baseline levels at 39 h postinjection. TDM was also able to induce IFN-.gamma. expression; however, kinetics of induction of IFN-.gamma. was different from that of IL-12p40. Maximal levels of IFN-.gamma. mRNA were reached by 24 h and did not return to baseline by 4 days. In addition, pretreatment of mice with neutralizing monoclonal antibodies directed against IL-12 (C15.6.7 and C15.1.2) blocked IFN-.gamma. mRNA induction in PEC from TDM-treated mice. We further determined if the induction of IL-12 and/or IFN-.gamma. contributes to the in vivo priming effect of TDM on peritoneal M.phi.. TDM-injected mice were treated in vivo with anti-IL-12 or anti-IFN-.gamma. (XMG.1.6) monoclonal antibodies. TDM-primed M.phi. were then activated in vitro with LPS and tested for their ability

to produce NO and to develop cytostatic activity toward cocultivated
L1210

tumor cells. Priming of M.phi. by TDM was completely blocked by in vivo neutralization of either IL-12 or IFN-.gamma. as demonstrated by an absence of tumoricidal activity and NO production by TDM-elicited M.phi. in the presence of LPS. Taken together our results show that TDM, a defined molecule from M. tuberculosis, induces in vivo production of IL-12. Moreover, synthesis of IL-12 mediates TDM priming of mouse peritoneal M.phi. through IFN- .gamma. induction.

CT Medical Descriptors:

*macrophage activation
*protein synthesis regulation
animal cell
article
bacterial cell wall
female
gene expression regulation
immunoregulation
immunostimulation
interferon production
mouse
mycobacterium
nonhuman
peritoneum macrophage
priority journal
Drug Descriptors:
***interleukin 12**
gamma interferon
messenger rna
nitric oxide
trehalose

L21 ANSWER 8 OF 13 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.

AN 97102127 EMBASE

DN 1997102127

TI Expression of cytokines and inducible nitric oxide synthase mRNA in the lungs of mice infected with Cryptococcus neoformans: Effects of interleukin- 12.

AU Kawakami K.; Tohyama M.; Qifeng X.; Saito A.

CS K. Kawakami, First Dept. of Internal Medicine, Faculty of Medicine, University of Ryukyus, 207 Uehara, Nishihara, Okinawa 903-01, Japan

SO Infection and Immunity, (1997) 65/4 (1307-1312).

Refs: 51

ISSN: 0019-9567 CODEN: INFIBR

CY United States

DT Journal; Article

FS 004 Microbiology

026 Immunology, Serology and Transplantation

LA English

SL English

AB We have recently established a murine model of pulmonary and disseminated infection with a highly virulent strain of Cryptococcus neoformans and demonstrated that administration of interleukin-12 (IL-12) protected the animals against infection. In this study, we extended these studies by investigating the host defense mechanisms. In particular, we examined the expression of mRNA for helper T-cell 1 (Th1) cytokines (IL-2, lymphotoxin,

and gamma interferon [IFN-.gamma.]), Th2 cytokines (IL-4, -6, and - 10), macrophage-derived cytokines (tumor necrosis factor alpha [TNF-.alpha.], IL- 1.beta., transforming growth factor .beta. [TGF-.beta.], IL-12p40, and IFN-.gamma.-inducing factor [IGIF]), and inducible nitric oxide synthase (iNOS) in the lungs on days 1, 3, 7, and 14 after infection and following treatment with IL-12. There was little or no expression of mRNAs for Th1 cytokines, TNF-.alpha., IL- 12p40, IGIF, and iNOS in the infected mice, but expression increased markedly after treatment with IL-12. In contrast,

the mRNAs for Th2 cytokines, IL- 1.beta., and TGF-.beta. were detected at considerable levels during the early stages of infection, and, interestingly, expression was not suppressed by IL-12 but rather augmented, particularly during the late stage. Similar results were also obtained for IFN-.gamma., IL-4, IL-10, and TNF-.alpha. measured in the lung homogenates by enzyme-linked immunosorbent assay. These results suggest that the predominance of expression of Th2 cytokines and TGF-.beta. over Th1 cytokines, TNF-.alpha., IL-12p40, IGIF, and iNOS is associated with severe lethal infection in mice and that administration

of IL-12 protects infected animals by stimulating Th1 cytokines.

CT Medical Descriptors:

- *cryptococcosis
- *host resistance
- *infection resistance
- *lung mycosis
- animal experiment
- animal model
- article
- cryptococcus neoformans
- enzyme induction
- female
- gene expression regulation
- helper cell
- immunoregulation
- immunostimulation**
- interferon production
- mouse
- nonhuman
- priority journal

Drug Descriptors:

- *gamma interferon: EC, endogenous compound
- *interleukin 12: EC, endogenous compound**
- *interleukin 1beta: EC, endogenous compound
- *interleukin 4: EC, endogenous compound
- *interleukin 6: EC, endogenous compound
- *nitric oxide synthase: EC, endogenous compound**
- interleukin 10: EC, endogenous compound
- messenger rna: EC, endogenous compound
- tumor necrosis factor alpha: EC, endogenous compound

L21 ANSWER 9 OF 13 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.

AN 97000667 EMBASE

DN 1997000667

TI Immune responses to parasites: The art of distinguishing the good from the bad.

AU Moll H.
 CS H. Moll, Res. Center for Infectious Diseases, University of Wurzburg,
 Rontgenring 11, D-97070 Wurzburg, Germany
 SO Immunology Today, (1996) 17/12 (551-552).
 ISSN: 0167-5699 CODEN: IMTOD8
 CY United Kingdom
 DT Journal; (Short Survey)
 FS 004 Microbiology
 026 Immunology, Serology and Transplantation
 LA English
 CT Medical Descriptors:
 *immune response
 *leishmania major
 *parasitosis: ET, etiology
 *parasitosis: DT, drug therapy
 *schistosoma mansoni
 *t lymphocyte
 *vaccination
 gene control
 mouse
 nonhuman
 priority journal
 short survey
 Drug Descriptors:
 *gamma interferon: EC, endogenous compound
 *interleukin 12: EC, endogenous compound
 *interleukin 4: EC, endogenous compound
 *nitric oxide: EC, endogenous compound
 *parasite antigen: EC, endogenous compound
 *tumor necrosis factor alpha: EC, endogenous compound

L21 ANSWER 10 OF 13 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
 AN 96233303 EMBASE
 DN 1996233303
 TI Interleukin-12 gene-expression of macrophages is regulated by nitric
 oxide.
 AU Rothe H.; Hartmann B.; Geerlings P.; Kolb H.
 CS Diabetes Research Institute, Heinrich- Heine Univ. of Dusseldorf, Auf'm
 Hennekamp 65,D-40225 Dusseldorf, Germany
 SO Biochemical and Biophysical Research Communications, (1996) 224/1
 (159-163).
 ISSN: 0006-291X CODEN: BBRCA
 CY United States
 DT Journal; Article
 FS 022 Human Genetics
 026 Immunology, Serology and Transplantation
 029 Clinical Biochemistry
 LA English
 SL English
 AB Interleukin-12 is a heterodimeric cytokine, mainly produced by
 macrophages. In our present study we demonstrate that interleukin-12
 expression is regulated by nitric oxide. Incubation of the macrophage
 cell line IC 21 with interferon-.gamma. gave rise to both interleukin-12 p40
 mRNA and nitric oxide production. The concurrent addition of the nitric
 oxide synthase inhibitor N(G)-monomethyl-L-arginine inhibited nitrite
 production and in parallel completely suppressed interleukin-12 p40 mRNA

formation. This indicated that endogenous nitric oxide synthase activity was required for IL-12 p40 gene expression. Exposure of the cells towards the nitric oxide generating compounds nitroprusside or S-nitroso-N-acetyl-penicillamine induced interleukin-12 p40 mRNA. Maximal mRNA levels were induced with nitric oxide donors at 1 .mu.M concentration. We conclude that nitric oxide may exert an autoregulatory and paracrine control of interleukin-12 gene expression.

CT Medical Descriptors:

*gene expression regulation

animal cell

article

controlled study

gene induction

macrophage

mouse

nonhuman

priority journal

Drug Descriptors:

***interleukin 12**

*nitric oxide: EC, endogenous compound

gamma interferon

messenger rna: EC, endogenous compound

n acetyl s nitrosopenicillamine

n(g) methylarginine

nitric oxide synthase inhibitor

nitroprusside sodium

L21 ANSWER 11 OF 13 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.

AN 96157564 EMBASE

DN 1996157564

TI Indirect stimulatory effects of murine interleukin-12 on in vitro production of nitric oxide by mouse peritoneal cells.

AU Zidek Z.; Lotzova E.; Frankova D.; Savary C.A.

CS Department of Surgical Oncology, Texas Univ. M.D. Anderson Can. Ctr., Box 18, 1515 Holcombe Boulevard, Houston, TX 77030, United States

SO Journal of Interferon and Cytokine Research, (1996) 16/5 (389-393).

ISSN: 1079-9907 CODEN: JICRFJ

CY United States

DT Journal; Article

FS 026 Immunology, Serology and Transplantation

037 Drug Literature Index

LA English

SL English

AB The effect of murine interleukin- 12 (IL-12) on L-arginine-dependent biosynthesis of nitric oxide (NO) by mouse peritoneal cells was evaluated.

Interleukin-12 was found to trigger considerably enhanced production of NO in a dose-dependent manner. Antibody neutralization studies indicated that

the effect of IL-12 was mediated by IFN-.gamma. without apparent participation of TNF- .alpha.. Synergistic effects of IL-12 plus lipopolysaccharide (LPS) were also observed. Our data thus provide evidence that IL-12 is a powerful but indirect modulator of NO formation. These findings may contribute to the better understanding of various biologic effects of IL-12.

CT Medical Descriptors:

***immunostimulation**

animal cell
 animal experiment
 animal tissue
 antibody production
 article
 controlled study
 dose response
 drug mechanism
 drug potentiation
 female
 immunopharmacology
 mouse
 nonhuman
 peritoneum cell
 priority journal
 Drug Descriptors:
 *interferon antibody: PD, pharmacology
 *interleukin 12: IT, drug interaction
 *interleukin 12: PD, pharmacology
 *n(g) methylarginine: PD, pharmacology
 *nitric oxide: EC, endogenous compound
 *tumor necrosis factor antibody: PD, pharmacology
 arginine: PD, pharmacology
 gamma interferon: EC, endogenous compound
 lipopolysaccharide: IT, drug interaction
 lipopolysaccharide: PD, pharmacology
 tumor necrosis factor alpha: EC, endogenous compound

L21 ANSWER 12 OF 13 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.

AN 96031280 EMBASE

DN 1996031280

TI Production of nitric oxide (NO) is not essential for protection against acute Toxoplasma gondii infection in IRF-1(-/-) mice.

AU Khan I.A.; Matsuura T.; Fonseka S.; Kasper L.H.

CS Department of Medicine, Dartmouth Medical School, Hanover, NH 03755, United States

SO Journal of Immunology, (1996) 156/2 (636-643).

ISSN: 0022-1767 CODEN: JOIMA3

CY United States

DT Journal; Article

FS 004 Microbiology

026 Immunology, Serology and Transplantation

030 Pharmacology

037 Drug Literature Index

LA English

SL English

AB Production of nitric oxide (NO) by macrophages is important for the killing of intracellular pathogens. IFN- γ and LPS stimulate NO production by transcriptional up-regulation of inducible nitric oxide synthetase (iNOS). In the present study we used mice with a targeted disruption of the IFN regulatory factor-1 gene (IRF-1(-/-)) to

investigate

the importance of NO in the host immune response against Toxoplasma gondii, a major cause of infection in newborns and those with AIDS. IRF-1(-/-) mice were more susceptible to acute Toxoplasma infection, and

treatment with either exogenous IFN- γ . or in vivo neutralization of endogenous IFN- γ . had little effect on their susceptibility to infection. However, administration of exogenous IL-12 was able to prolong survival even when IFN- γ . was depleted. An in vivo depletion study suggested that the mechanism of this protective response is mediated in part by CD4⁺ T cells. The administration of IL-12 could not overcome the inhibition of lymphoproliferative response in T. gondii-infected mice and treatment with N-monomethyl-L-arginine (L-NMMA), a nitric oxide synthase (iNOS) antagonist in vitro was unable to reverse the immunosuppression.

In

response to Toxoplasma infection, splenocytes from IRF-1(-/-) mice exhibited increased production of IL-10 as well as a 30-fold increase in its message expression. These studies indicate that NO may not be essential for host immunity to the parasite, and moreover that IL-12 appears to induce an IFN- γ .-independent mechanism of protection against this opportunistic pathogen.

CT

Medical Descriptors:

*regulator gene
 *toxoplasma gondii
 *toxoplasmosis: PC, prevention
 animal cell
 animal experiment
 animal model
 article
 controlled study
 depletion
 female
 gene disruption
 infection sensitivity
 lymphocyte proliferation
 mouse
 nonhuman
 priority journal
 survival
 Drug Descriptors:
 *cd4 antigen: EC, endogenous compound
 *gamma interferon
 *interleukin 12
 *n(g) methylarginine
 *nitric oxide: EC, endogenous compound
 *nitric oxide synthase inhibitor
 cd8 antigen: EC, endogenous compound
 concanavalin a
 immunoglobulin g
 interferon antibody
 interleukin 10: EC, endogenous compound
 messenger rna: EC, endogenous compound
 nitrite: EC, endogenous compound

L21 ANSWER 13 OF 13 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
 AN 95267825 EMBASE
 DN 1995267825
 TI IL-12-induced protection against blood-stage Plasmodium chabaudi AS
 requires IFN- γ . and TNF- α . and occurs via a nitric
 oxide-dependent mechanism.
 AU Stevenson M.M.; Mi Fong Tam; Wolf S.F.; Sher A.
 CS Montreal Gen. Hosp. Research Inst., 1650 Cedar Avenue, Montreal, Que. H3G
 Page 137

1A4, Canada
SO Journal of Immunology, (1995) 155/5 (2545-2556).
ISSN: 0022-1767 CODEN: JOIMA3
CY United States
DT Journal; Article
FS 026 Immunology, Serology and Transplantation
LA English
SL English
AB The effects of IL-12 administration on the development of protective
of immunity to blood-stage Plasmodium chabaudi AS were analyzed. Treatment
the susceptible A/J mice on the day of infection and for 5 days postinfection
with various doses (0.025-0.3 .mu.g) of rIL-12 significantly decreased
peak parasitemia level, but only treatment with 0.1 .mu.g resulted in
increased survival. Treatment of resistant 86 mice with 0.1 .mu.g of
rIL-12 using the same regimen also significantly decreased the peak
parasitemia level, but 40% of the animals died. Treatment of these mice
with anti-IL-12 mAb resulted in a more severe course of infection, but
survival was not significantly altered. The mechanism of IL-12-induced
resistance was examined in A/J mice during infection. Compared with
spleen cells from untreated mice, cells from IL-12-treated mice produced
significantly higher levels of IFN-.gamma. spontaneously as well as in
response to Con A or Ag stimulation on day 7 postinfection. Significantly
higher levels of IFN-.gamma. and TNF-.alpha. were found in the sera of
IL-12-treated mice, which correlated with high levels of the nitric oxide
(NO) metabolite, NO3-. Furthermore, CD4+ T cell depletion was found to
abrogate IL-12-induced resistance. Administration of neutralizing mAb
against IFN-.gamma. or TNF-.alpha. to IL-12-treated mice showed that
simultaneous depletion of both cytokines resulted in 100% mortality. The
role of NO was investigated by administration of aminoguanidine, a
selective inhibitor of cytokine-inducible nitric oxide synthase, to
IL-12-treated mice. Significantly increased mortality was observed
following treatment twice daily with 9 mg of aminoguanidine, but there
was no effect on parasitemia. In conclusion, these results demonstrate that
IL-12 regulates the development of resistance to P. chabaudi AS via a
CD4+ Th1 response, which involves the cytokines IFN-.gamma. and TNF-.alpha.,
and is in part NO dependent. Therefore, IL-12, given in the appropriate
dose, may be useful in the induction of protective immunity to
blood-stage malaria.
CT Medical Descriptors:
*malaria: ET, etiology
animal experiment
antimalarial activity
article
controlled study
female
immunostimulation
infection resistance
male
mouse
nonhuman
plasmodium chabaudi

priority journal

Drug Descriptors:

*gamma interferon: EC, endogenous compound

*interleukin 12: EC, endogenous compound

*nitric oxide: EC, endogenous compound

*tumor necrosis factor alpha: EC, endogenous compound

L22 ANSWER 1 OF 27 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
 AN 2000342967 EMBASE
 TI The combined action of IL-15 and IL-12 gene transfer can induce tumor cell rejection without T and NK cell involvement.
 AU Di Carlo E.; Comes A.; Basso S.; De Ambrosio A.; Meazza R.; Musiani P.; Moelling K.; Albini A.; Ferrini S.
 CS Dr. S. Ferrini, Centro di Biotecnologie Avanzate, Largo Rosanna Benzi no. 10, 16132 Genova, Italy. ferrini@ermes.cba.unige.it
 SO Journal of Immunology, (15 Sep 2000) 165/6 (3111-3118).
 Refs: 56
 ISSN: 0022-1767 CODEN: JOIMA3
 CY United States
 DT Journal; Article
 FS 026 Immunology, Serology and Transplantation
 LA English
 SL English
 AB The cooperative antitumor effects of IL-12 and IL-15 gene transfer were studied in the N592 MHC class I-negative small cell lung cancer cell line xenotransplanted in nude mice. N592 cells engineered to secrete IL-15 displayed a significantly reduced tumor growth kinetics, and a slightly reduced tumor take rate, while N592 engineered with IL-12 displayed only minor changes in their growth in nude mice. However, N592 cells producing both cytokines were completely rejected, and produced a potent local bystander effect, inducing rejection of coinjected wild-type tumor cells. N592/IL-12/IL-15 cells were completely and promptly rejected also in NK-depleted nude mice, while in granulocyte-depleted animals a slight delay in the rejection process was observed. Immunohistochemical analyses of the N592/IL-12/IL-15 tumor area in intact nude mice revealed the presence of infiltrating macrophages, granulocytes, and NK cells, and expression of inducible NO synthase and of secondary cytokines such as IL-1.beta., TNF-.alpha., and IFN-.gamma., and at higher levels GM-CSF, macrophage-inflammatory protein-2, and monocyte chemoattractant protein-1.
 In NK cell-depleted nude mice, numerous macrophages and granulocytes infiltrated the tumor, and a strong expression of macrophage-inflammatory protein-2 and inducible NO synthase was also observed. Finally, macrophages cocultured with N592/IL-12/IL-15 produced NO in vitro, and **inhibited** tumor cell growth, further suggesting their role as effector cells in this model.
 CT Medical Descriptors:
 *gene transfer
 *natural killer cell
 *major histocompatibility complex
 *tumor immunity
 *T lymphocyte
 nude mouse

lung small cell cancer
 tumor growth
 xenograft
 antineoplastic activity
 protein expression
 effector cell
 immunohistochemistry
 gene therapy
 nonhuman
 animal experiment
 animal model
 animal cell
 article
 priority journal
 Drug Descriptors:
 *interleukin 15
 *interleukin 12
 nitric oxide synthase: EC, endogenous compound
 macrophage inflammatory protein 2: EC, endogenous compound
 interleukin 1beta

L22 ANSWER 2 OF 27 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
 AN 2000166948 EMBASE
 TI Blockade of costimulation prevents infection-induced immunopathology in interleukin-10-deficient mice.
 AU Villegas E.N.; Wille U.; Craig L.; Linsley P.S.; Rennick D.M.; Peach R.; Hunter C.A.
 CS C.A. Hunter, Department of Pathobiology, University of Pennsylvania, School of Veterinary Medicine, 3800 Spruce St., Philadelphia, PA 19104-6008, United States. chunter@phl.vet.upenn.edu
 SO Infection and Immunity, (2000) 68/5 (2837-2844).
 Refs: 56
 ISSN: 0019-9567 CODEN: INFIBR
 CY United States
 DT Journal; Article
 FS 004 Microbiology
 005 General Pathology and Pathological Anatomy
 026 Immunology, Serology and Transplantation
 LA English
 SL English
 AB Interleukin-10 (IL-10) is associated with **inhibition** of cell-mediated immunity and downregulation of the expression of costimulatory molecules required for T-cell activation. When IL-10-deficient (IL-10KO) mice are infected with *Toxoplasma gondii*, they succumb to a T-cell-mediated shock-like reaction characterized by the overproduction of IL-12 and gamma interferon (IFN- γ) associated with widespread necrosis of the liver. Since costimulation is critical for T-cell activation, we investigated the role of the CD28-B7 and CD40-CD40 ligand (CD40L) interactions in this infection-induced immunopathology. Our studies show that infection of mice with *T. gondii* resulted in increased expression of B7 and CD40 that was similar in wild-type and IL-10KO mice. In vivo blockade of the CD28-B7 or CD40-CD40L interactions following infection of IL-10KO mice with *T. gondii* did not affect serum levels of IFN- γ or IL-12, nor did it prevent death in these mice. However, when both pathways were blocked, the IL-10KO mice survived the acute phase of infection and had reduced serum levels of IFN- γ and alanine

transaminase as well as decreased expression of inducible nitric oxide synthase in the liver and spleen. Analysis of parasite-specific recall responses from infected IL-10KO mice revealed that blockade of the CD40-CD40L interaction had minimal effects on cytokine production, whereas blockade of the CD28-B7 interaction resulted in decreased production of IFN- γ . but not IL-12. Further reduction of IFN- γ production was observed when both costimulatory pathways were blocked. Together, these results demonstrate that the CD28-B7 and CD40-CD40L interactions are involved in the development of infection-induced immunopathology in the absence of IL-10.

CT Medical Descriptors:
 *immunopathology
 *toxoplasmosis
 *T lymphocyte activation
 cellular immunity
 down regulation
 Toxoplasma gondii
 cytokine production
 antigen expression
 cytotoxic T lymphocyte
 nonhuman
 female
 mouse
 animal experiment
 animal model
 controlled study
 animal tissue
 article
 priority journal
 Drug Descriptors:
 *interleukin 10
***interleukin 12: EC, endogenous compound**
 *gamma interferon: EC, endogenous compound
 *CD28 antigen: EC, endogenous compound
 *CD40 antigen: EC, endogenous compound
nitric oxide synthase: EC, endogenous compound
 alanine aminotransferase: EC, endogenous compound

L22 ANSWER 3 OF 27 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
 AN 1999435728 EMBASE
 TI Extracellular signal-related kinase (ERK) and p38 mitogen-activated protein (MAP) kinases differentially regulate the lipopolysaccharide-mediated induction of inducible nitric oxide synthase and IL-12 in macrophages: Leishmania phosphoglycans subvert macrophage IL-12 production by targeting ERK MAP kinase.
 AU Feng G.-J.; Goodridge H.S.; Harnett M.M.; Wei X.-Q.; Nikolaev A.V.; Higson A.P.; Liew F.-Y.
 CS Dr. F.-Y. Liew, Department of Immunology, University of Glasgow, Glasgow G11 6NT, United Kingdom. f.y.liew@clinmed.gla.ac.uk
 SO Journal of Immunology, (1999) 163/12 (6403-6412).
 Refs: 55
 ISSN: 0022-1767 CODEN: JOIMA3
 CY United States

DT Journal; Article
 FS 004 Microbiology
 026 Immunology, Serology and Transplantation
 LA English
 SL English
 AB Macrophage activation by cytokines or microbial products such as LPS results in the induction and release of several key immune effector molecules including NO and IL-12. These have been shown to play crucial roles in the development of immunity to intracellular pathogens such as Leishmania. The molecular mechanisms underlying the induction of these effector molecules are not fully understood. We now show that the extracellular signal-related kinase (ERK) and p38 mitogen-activated protein (MAP) kinases play differential roles in the regulation of LPS-stimulated inducible NO synthase and IL-12 gene expression. In macrophages, LPS stimulates the simultaneous activation of all three classes of MAP kinases, ERK, c-jun N-terminal kinase, and p38, albeit with differential activation kinetics. However, studies using **inhibitors** selective for ERK (PD98059) and p38 (SB203580) show that while p38 plays an essential role in the induction of inducible NO synthase, ERK MAP kinases play only a minor role in promoting NO generation. In contrast, while p38 promotes induction of IL-12 (p40) mRNA, ERK activation suppresses LPS-mediated IL-12 transcription. The biological relevance of these regulatory signals is demonstrated by our finding that Leishmania lipophosphoglycans, which promote parasite survival, act by stimulating ERK MAP kinase to **inhibit** macrophage IL-12 production. Thus, as ERK and p38 MAP kinases differentially regulate the induction of the macrophage effector molecules, inducible NO synthase and IL-12, these kinases are potential targets not only for the development of novel strategies to combat intracellular pathogens but also for therapeutic immunomodulation.

CT Medical Descriptors:
 *cytokine production
 *leishmaniasis
 *immunomodulation
 peritoneum macrophage
 enzyme induction
 protein targeting
 macrophage activation
 inflammation
 parasite survival
 nonhuman
 mouse
 controlled study
 animal cell
 article
 priority journal
 Drug Descriptors:
 *mitogen activated protein kinase
 *synaptophysin
 *interleukin 12
 *lipophosphoglycan
 *nitric oxide synthase
 lipopolysaccharide

AN 1999431448 EMBASE
 TI Antifungal type 1 responses are upregulated in IL-10-deficient mice.
 AU Del Sero G.; Mencacci A.; Cenci E.; D'Ostiani C.F.; Montagnoli C.; Bacci A.; Mosci P.; Kopf M.; Romani L.
 CS L. Romani, Microbiology Section, Dept. of Exp. Med. and Biochem. Sci., University of Perugia, I-06122 Perugia, Italy
 SO Microbes and Infection, (1999) 1/14 (1169-1180).
 Refs: 82
 ISSN: 1286-4579 CODEN: MCINFS
 CY France
 DT Journal; Article
 FS 004 Microbiology
 026 Immunology, Serology and Transplantation
 LA English
 SL English
 AB C57BL/6 mice are highly resistant to infections caused by *Candida albicans* and *Aspergillus fumigatus*. To elucidate the role of IL-10 produced by C57BL/6 mice during these infections, parameters of infection and immunity to it were evaluated in IL-10-deficient and wild-type mice with disseminated or gastrointestinal candidiasis or invasive pulmonary aspergillosis. Unlike parasitic protozoan infection, *C. albicans* or *A. fumigatus* infection did not induce significant acute toxicity in IL-10-deficient mice, who, instead, showed reduced fungal burden and fungal-associated inflammatory responses. The increased resistance to infections as compared to wild-type mice was associated with upregulation of innate and acquired antifungal Th1 responses, such as a dramatically higher production of IL-12, nitric oxide (NO) and TNF- α as well as IFN- γ by CD4+ T cells. Pharmacological inhibition of NO production greatly reduced resistance to gastrointestinal candidiasis, thus pointing to the importance of IL-10-dependent NO regulation at mucosal sites in fungal infections. These results are reminiscent of those obtained in genetically susceptible mice, in which IL-10 administration increased, and IL-10 neutralization decreased, susceptibility to *C. albicans* and *A. fumigatus* infections. Collectively, these observations indicate that the absence of IL-10 augments innate and acquired antifungal immunity by upregulating type 1 cytokine responses. The resulting protective Th1 responses lead to a prompt reduction of fungal growth, thus preventing tissue destruction and lethal levels of proinflammatory cytokines.

CT Medical Descriptors:
 *immune response
 *cytokine production
 *candidiasis: ET, etiology
 *lung aspergillosis: ET, etiology
 helper cell
 knockout mouse
 infection resistance
 candida albicans
 aspergillus fumigatus
 inflammation
 genetic susceptibility
 cellular immunity

nonhuman
male
female
mouse
animal experiment
animal model
animal tissue
animal cell
article
priority journal
Drug Descriptors:
***interleukin 12: EC, endogenous compound**
nitric oxide: EC, endogenous compound
tumor necrosis factor alpha: EC, endogenous compound
gamma interferon: EC, endogenous compound

L22 ANSWER 5 OF 27 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN 1999267907 EMBASE
TI IL-12 as a therapeutic target for pharmacological modulation in
immune-mediated and inflammatory diseases: Regulation of T helper 1/T
helper 2 responses.
AU Hasko G.; Szabo C.
CS G. Hasko, Inotek Corp, 100 Cummings Center, Beverly, Massachusetts, MA
01915, United States. ghasko@inotekcorp.com
SO British Journal of Pharmacology, (1999) 127/6 (1295-1304).
Refs: 129
ISSN: 0007-1188 CODEN: BJPCBM
CY United Kingdom
DT Journal; General Review
FS 026 Immunology, Serology and Transplantation
030 Pharmacology
037 Drug Literature Index
LA English
SL English
AB 1. Interleukin-12 (IL-12) is a pivotal cytokine in driving the immune
system towards a T helper (Th)1 type response and preventing a Th2 type
immune profile. Therefore, IL-12 is indispensable in the defense against
certain, mainly intracellular pathogens, but overproduction of this
cytokine is crucially involved in the etiology of several inflammatory
and
autoimmune diseases. 2. Hence, IL-12 is an ideal target for
pharmacological intervention in the therapy of autoimmune and
inflammatory
diseases. 3. The production of IL-12 and a resultant Th1 type immune
response can be suppressed with several pharmacological approaches
including modulation of intracellular cyclic AMP levels, glucocorticoids
and nuclear factor- κ B inhibition. IL-12 responsiveness may
be inhibited using anti-IL-12 antibodies, soluble IL-12
receptors or the IL-12 p46 homodimer. 4. Exploitation of these approaches
may provide novel means for the experimental therapy of a variety of
pathophysiological states.
CT Medical Descriptors:
*immunomodulation
*immunopathology
*inflammation
*helper cell
cellular immunity

host resistance
 autoimmune disease: ET, etiology
 drug targeting
 signal transduction
 human
 nonhuman
 review
 priority journal
 Drug Descriptors:
***interleukin 12: EC, endogenous compound**
 cyclic AMP: EC, endogenous compound
 glucocorticoid: DV, drug development
 glucocorticoid: PD, pharmacology
 immunoglobulin enhancer binding protein: EC, endogenous compound
 interleukin 12 receptor: DV, drug development
 protein p40: DV, drug development
 protein p40: PD, pharmacology
 cytokine antibody: DV, drug development
 cytokine antibody: PD, pharmacology
nitric oxide: EC, endogenous compound
 immunosuppressive agent: DV, drug development
 immunosuppressive agent: PD, pharmacology
 salbutamol: PD, pharmacology
 prostaglandin e2: PD, pharmacology
 calcitonin gene related peptide: PD, pharmacology
 dexamethasone: PD, pharmacology
 hydrocortisone: PD, pharmacology
 clobetasol: PD, pharmacology
 acetylsalicylic acid: PD, pharmacology
 n(g) methylarginine: PD, pharmacology
 captopril: PD, pharmacology
 lisinopril: PD, pharmacology
 adenosine: PD, pharmacology
 glibenclamide: PD, pharmacology

L22 ANSWER 6 OF 27 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
 AN 1999232937 EMBASE
 TI Macrophage control of herpes simplex virus type 1 replication in the
 peripheral nervous system.
 AU Kodukula P.; Liu T.; Van Rooijen N.; Jager M.J.; Hendricks R.L.
 CS Dr. R.L. Hendricks, Univ. of Pittsburgh Sch. of Medicine, 915 Eye and Ear
 Institute, 203 Lothrop Street, Pittsburgh, PA 15213-2588, United States.
 hendricksRR@MSX.UPMC.edu
 SO Journal of Immunology, (1 Mar 1999) 162/5 (2895-2905).
 Refs: 24
 ISSN: 0022-1767 CODEN: JOIMA3
 CY United States
 DT Journal; Article
 FS 004 Microbiology
 008 Neurology and Neurosurgery
 026 Immunology, Serology and Transplantation
 LA English
 SL English
 AB After corneal infection, herpes simplex virus type 1 (HSV-1) invades
 sensory neurons with cell bodies in the trigeminal ganglion (TG),
 replicates briefly, and then establishes a latent infection in these
 neurons. HSV-1 replication in the TG can be detected as early as 2 days

after corneal infection, reaches peak titers by 3-5 days after infection, and is undetectable by 7-10 days. During the period of HSV-1 replication, macrophages and .gamma..delta. TCR+ T lymphocytes infiltrate the TG, and TNF-.alpha., IFN-.gamma., the inducible nitric oxide synthase (iNOS) enzyme, and IL-12 are expressed. TNF-.alpha., IFN-.gamma., and the iNOS product nitric oxide (NO) all **inhibit** HSV-1 replication in vitro. Macrophage and .gamma..delta. TCR+ T cell depletion studies demonstrated that macrophages are the main source of TNF-.alpha. and iNOS,

whereas .gamma..delta. TCR+ T cells produce IFN-.gamma.. Macrophage depletion, aminoguanidine **inhibition** of iNOS, and neutralization of TNF-.alpha. or IFN-.gamma. all individually and synergistically increased HSV-1 titers in the TG after HSV-1 corneal infection.

Moreover, individually depleting macrophages or neutralizing TNF-.alpha. or IFN-.gamma. markedly reduced the accumulation of both macrophages and .gamma..delta. TCR+ T cells in the TG. Our findings establish that after primary HSV-1 infection, the bulk of virus replication in the sensory ganglia is controlled by macrophages and .gamma..delta. TCR+ T

lymphocytes through their production of antiviral molecules TNF-.alpha., NO, and IFN-.gamma.. Our findings also strongly suggest that cross-regulation between these two cell types is necessary for their accumulation and function in the infected TG.

CT Medical Descriptors:

- *herpes simplex virus 1
- *peripheral nervous system
- *virus replication
- macrophage
- trigeminus ganglion
- eye infection
- t lymphocyte
- interferon production
- nonhuman
- female
- mouse
- animal experiment
- animal cell
- article
- priority journal

Drug Descriptors:

- *t lymphocyte receptor: EC, endogenous compound
- *tumor necrosis factor alpha: EC, endogenous compound
- *gamma interferon: EC, endogenous compound
- ***nitric oxide synthase: EC, endogenous compound**
- ***interleukin 12: EC, endogenous compound**

L22 ANSWER 7 OF 27 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.

AN 1999231196 EMBASE

TI Different doses of adenoviral vector expressing IL-12 enhance or depress the immune response to a coadministered antigen: The role of nitric oxide.

AU Lasarte J.J.; Corrales F.J.; Casares N.; De Cerio A.L.-D.; Qian C.; Xie X.; Borrás-Cuesta F.; Prieto J.

CS Dr. J. Prieto, Department of Medicine, Liver Unit, University of Navarra, 31008 Pamplona, Spain. jprieto@unav.es

SO Journal of Immunology, (1 May 1999) 162/9 (5270-5277).

Refs: 50
 ISSN: 0022-1767 CODEN: JOIMA3

CY United States
 DT Journal; Article
 FS 026 Immunology, Serology and Transplantation
 037 Drug Literature Index
 LA English
 SL English
 AB Joint immunization with two recombinant adenoviruses, one expressing hepatitis C virus (HCV) core and E1 proteins and another expressing IL-12 (RAdIL-12), strongly potentiates cellular immune response against HCV Ags in BALB/c mice when RAdIL-12 was used at doses of 1×10^5 - 1×10^7 plaque-forming units. However, cellular immunity against HCV Ags was abolished when higher doses (1×10^8 plaque-forming units) of RAdIL-12 were used. This immunosuppressive effect was associated with marked elevation of IFN- γ and nitric oxide in the serum and increased cell apoptosis in the spleen. Administration of N-nitro-L-arginine methyl ester (L-NAME),
 an **inhibitor** of nitric oxide synthase, to mice that received high doses of RAdIL-12 was lethal, whereas no apparent systemic toxicity by L-NAME was observed in those immunized with lower doses of the
 adenovirus.
 Interestingly, in mice immunized with recombinant adenovirus expressing core and E1 proteins of HCV in combination with RAdIL-12 at low doses (1×10^7 plaque-forming units), L-NAME **inhibited** T cell proliferation and CTL activity in response to HCV Ags and also production of Abs against adenoviral proteins. In conclusion, gene transfer of IL-12 can increase or abolish cell immunity against an Ag depending of the dose of the vector expressing the cytokine. IL-12 stimulates the synthesis of NO which is needed for the immunostimulating effects of IL-12, but apoptosis of T cells and immunosuppression ensues when IFN- γ and NO are generated at very high concentrations.

CT Medical Descriptors:
 *virus immunity
 *protein expression
 virus vector
 immune response
 hepatitis c virus
 dose response
 plaque forming cell
enzyme inhibition
 gene transfer
 cytokine production
 nonhuman
 mouse
 animal experiment
 controlled study
 animal tissue
 animal cell
 intraperitoneal drug administration
 article
 priority journal
 Drug Descriptors:
***interleukin 12: EC, endogenous compound**
 *virus antigen: EC, endogenous compound
 virus protein: EC, endogenous compound

gamma interferon: EC, endogenous compound
nitric oxide: EC, endogenous compound
interleukin 2: EC, endogenous compound
glutathione: EC, endogenous compound
n(g) nitroarginine methyl ester: DO, drug dose
n(g) nitroarginine methyl ester: PD, pharmacology

L22 ANSWER 8 OF 27 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN 1999192775 EMBASE
TI Immunopathology of inflammatory neuropathies.
AU Oka N.
CS Dr. N. Oka, Department of Neurology, Kyoto University Hospital, Kyoto, Japan
SO Clinical Neurology, (1999) 39/1 (90-91).
Refs: 7
ISSN: 0009-918X CODEN: RISHDJ
CY Japan
DT Journal; Conference Article
FS 005 General Pathology and Pathological Anatomy
008 Neurology and Neurosurgery
037 Drug Literature Index
LA Japanese
SL English; Japanese
AB With the use of immunohistochemical technique, nerve biopsy is more informative for the diagnosis of inflammatory neuropathies. In chronic inflammatory demyelinating neuropathy, an increased number of T cells are frequently present in endoneurium, which is in contrast to hereditary neuropathies. In active demyelinating lesions, macrophages adhering nerve fibers showed stainings with TNF-.alpha., NOS and cyclooxygenase-2 (COX-2). These molecules may act in concert to promote nerve damage. The **inhibitor** of COX- 2, nimesulide, was effective on experimental allergic neuritis, even if given after the onset of clinical signs. A COX-2 **inhibitor** may have potential as an additional therapeutic agent in human inflammatory neuropathies. In vasculitic neuropathies, cell-mediated cytotoxicity may be involved in the pathogenesis of small vessel injury. Axonal injury may be caused by focal ischemia. However, an immune attack might be involved in nerve damage, since T cells and IL-12 positive cells were found in endoneurium of some patients with active vasculitis.
CT Medical Descriptors:
*neuropathy: DI, diagnosis
*neuropathy: ET, etiology
*chronic inflammation: DI, diagnosis
*immunopathology
immunohistochemistry
nerve biopsy
demyelinating neuropathy: ET, etiology
t lymphocyte
endoneurium
familial disease
macrophage
allergic neuropathy: ET, etiology
vasculitis
cell mediated cytotoxicity
ischemia
human
nonhuman

conference paper

Drug Descriptors:

*nimesulide

*cyclooxygenase 2 inhibitor

*tumor necrosis factor alpha: EC, endogenous compound

*nitric oxide synthase: EC, endogenous compound

*cyclooxygenase 2: EC, endogenous compound

*interleukin 12: EC, endogenous compound

L22 ANSWER 9 OF 27 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.

AN 1999150689 EMBASE

TI Role of TNF-.alpha. in the induction of fungicidal activity of mouse peritoneal exudate cells against Cryptococcus neoformans by IL-12 and IL-18.

AU Kawakami K.; Qureshi M.H.; Koguchi Y.; Zhang T.; Okamura H.; Kurimoto M.; Saito A.

CS K. Kawakami, First Dept. of Internal Medicine, Faculty of Medicine, University of the Ryukyus, Okinawa 903-0215, Japan

SO Cellular Immunology, (10 Apr 1999) 193/1 (9-16).

Refs: 43

ISSN: 0008-8749 CODEN: CLIMB8

CY United States

DT Journal; Article

FS 026 Immunology, Serology and Transplantation

LA English

SL English

AB We have recently demonstrated that two IFN-.gamma.-inducing cytokines, interleukin (IL)-12 and IL-18, synergistically induced the fungicidal activity of mouse peritoneal exudate cells (PEC) against Cryptococcus neoformans through NK cell production of interferon (IFN)-.gamma. and nitric oxide (NO) synthesis. In the present study, we further dissected these effects by examining the involvement of tumor necrosis factor (TNF)-.alpha. in the induction of IL-12/IL-18-stimulated PEC fungicidal activity. The addition of neutralizing anti-TNF-.alpha. mAb significantly suppressed IL-12/IL-18-stimulated PEC anticryptococcal activity. This effect was ascribed to the **inhibition** of macrophage NO synthesis, but not of IFN-.gamma. production by NK cells, because the

same

treatment **inhibited** the former response, but not the latter one.

On the other hand, combined treatment with IL-12 and IL-18

synergistically

induced the production of TNF-.alpha. by PEC and this effect was almost completely abrogated by neutralizing anti-IFN-.gamma. mAb. The cell type producing TNF-.alpha. among PEC was mostly macrophage. TNF-.alpha. significantly promoted macrophage NO production and anticryptococcal activity induced by IFN-.gamma., and furthermore anti-TNF-.alpha. mAb partially **inhibited** these responses. Considered together, our results indicated that TNF-.alpha. contributed to the potentiation of IL-12/IL-18-induced PEC fungicidal activity against C. neoformans

through

enhancement of IFN-.gamma.-induced production of NO by macrophages, but not through increased production of IFN-.gamma. by NK cells.

CT Medical Descriptors:

*peritoneal exudate cell

*cryptococcus neoformans

fungicidal activity

cytokine production

macrophage
 natural killer cell
 nonhuman
 mouse
 controlled study
 animal cell
 article
 priority journal
 Drug Descriptors:
 *tumor necrosis factor alpha: EC, endogenous compound
 *interleukin 12: EC, endogenous compound
 *interleukin 18: EC, endogenous compound
 nitric oxide: EC, endogenous compound
 gamma interferon: EC, endogenous compound

L22 ANSWER 10 OF 27 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
 AN 1999101467 EMBASE
 TI Adenovirus-mediated interleukin-12 gene therapy for prostate cancer:
 Suppression of orthotopic tumor growth and pre-established lung
 metastases
 in an orthotopic model.
 AU Nasu Y.; Bangma C.H.; Hull G.W.; Lee H.-M.; Hu J.; Wang J.; McCurdy M.A.;
 Shimura S.; Yang G.; Timme T.L.; Thompson T.C.
 CS T.C. Thompson, Scott Department of Urology, Baylor College of Medicine,
 6560 Fannin, Houston, TX 77030, United States
 SO Gene Therapy, (1999) 6/3 (338-349).
 Refs: 42
 ISSN: 0969-7128 CODEN: GETHEC
 CY United Kingdom
 DT Journal; Article
 FS 016 Cancer
 022 Human Genetics
 028 Urology and Nephrology
 030 Pharmacology
 037 Drug Literature Index
 LA English
 SL English
 AB Interleukin-12 (IL-12) can elicit potent antitumoral effects that involve
 the recruitment of specific immune effector cells. We investigated the
 efficacy o a single injection of a recombinant adenovirus expressing
 murine IL-12 (AdmIL-12) directly into orthoptic mouse prostate
 carcinomas
 generated from a poorly immunogenic cell line (RM-9) derived from the
 mouse prostate reconstitution system. Significant growth suppression (>
 50% reduction of tumor weight) and increased mean survival time (23.4 to
 28.9 days) were observed compared with controls. Suppression of
 pre-established lung metastases was also observed following the injection
 of AdmIL-12 into the orthoptic tumor. Cytolytic natural killer cell
 activity was markedly enhanced 1-2 days after virus injection.
 Immunohistochemical analysis showed significantly elevated intratumoral
 infiltration of CD4+ and CD8+ T cells 7 days after virus injection.
 However, splenocyte-derived cytotoxic T lymphocytes were not detected
 during the 14 days following treatment. Increased numbers of nitric oxide
 synthase-positive macrophages were seen in the AdmIL-12 treated group 7
 days following injection. Systemic inhibition of natural killer
 cells with anti-asialo-GM1 serum led to increased numbers of lung
 metastases in AdmIL-12-treated orthotopic tumors but did not affect local

tumor growth. In this model system the anti-tumor effects of a single injection of adenovirus-mediated IL-12 appears to be based to a large extent on the activation of nitric oxide synthase in macrophages and possibly T cell activities, whereas the relatively early cytolytic activity of natural killer cells are largely but not exclusively responsible for the antimetastatic effects.

CT Medical Descriptors:

*gene therapy
 *prostate cancer: DT, drug therapy
 adenovirus
 tumor growth
 lung metastasis: CO, complication
 antineoplastic activity
 immunocompetent cell
growth inhibition
cancer inhibition
 survival time
 cancer survival
 immunohistochemistry
 cytotoxic t lymphocyte
 macrophage
 natural killer cell
 cytolysis
 enzyme activity
 cell infiltration
 antigen expression
 dose response
 nonhuman
 male
 mouse
 animal experiment
 animal model
 controlled study
 animal cell
 intratumoral drug administration
 article
 priority journal
 Drug Descriptors:
***interleukin 12: DT, drug therapy**
 cd4 antigen: EC, endogenous compound
 cd8 antigen: EC, endogenous compound
nitric oxide synthase: EC, endogenous compound
 major histocompatibility antigen class 1: EC, endogenous compound

L22 ANSWER 11 OF 27 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
 AN 1998417470 EMBASE
 TI Nitric oxide regulates Th1 cell development through the **inhibition**
 of IL-12 synthesis by macrophages.
 AU Huang F.-P.; Niedbala W.; Wei X.-Q.; Xu D.; Feng G.-J.; Robinson J.H.;
 Lam C.; Liew F.Y.
 CS F.Y. Liew, Department of Immunology, University of Glasgow, Glasgow G11
 6NT, United Kingdom. f.y.liew@clinmed.gla.ac.uk
 SO European Journal of Immunology, (1998) 28/12 (4062-4070).
 Refs: 41
 ISSN: 0014-2980 CODEN: EJIMAF
 CY Germany

DT Journal; Article
 FS 004 Microbiology
 026 Immunology, Serology and Transplantation
 029 Clinical Biochemistry
 LA English
 SL English
 AB We have previously reported that mice lacking inducible nitric oxide synthase (NOS2) developed enhanced Th1 cell responses. We now investigated the mechanism by which NO modulates Th1 cells differentiation. Peritoneal macrophages from NOS2-deficient mice infected with *Leishmania major* in vivo or stimulated with IFN- γ or lipopolysaccharide (LPS) in vitro produced significantly higher levels of IL-12 than those from heterozygous or wild-type mice. A macrophage cell line, J774, produced significant amounts of IL-12 following activation with LPS, or LPS plus IFN- γ . This could be markedly enhanced by the NOS inhibitor L-N(G) monomethyl arginine (L-NMMA), but profoundly inhibited by the NO-generating compound S-nitroso-N-acetyl-penicillamine (SNAP). The effect of NO in this system is selective, since SNAP enhanced and L-NMMA decreased TNF- α synthesis by LPS-activated J774 cells. The differential effect of NO on IL-12 and TNF- α is at the transcriptional level and is activation dependent. Since IL-12 is a major inducer of Th1 cells which produce IFN- γ that can activate macrophages to produce IL-12, our data demonstrate that NO can be an inhibitor of this feedback loop, preventing the excessive amplification of Th1 cells which are implicated in a range of immunopathologies.

CT Medical Descriptors:
 *helper cell
 *peritoneum macrophage
 cell differentiation
 leishmania major
 heterozygote
 feedback system
 nonhuman
 mouse
 animal experiment
 animal model
 controlled study
 animal cell
 article
 priority journal
 Drug Descriptors:
 *nitric oxide: EC, endogenous compound
 *interleukin 12: EC, endogenous compound
 gamma interferon
 lipopolysaccharide
 n(g) methylarginine
 n acetyl s nitrosopenicillamine
 tumor necrosis factor alpha: EC, endogenous compound

L22 ANSWER 12 OF 27 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
 AN 1998368426 EMBASE
 TI An agonist of adenosine A3 receptors decreases interleukin-12 and interferon- γ production and prevents lethality in endotoxemic mice.

AU Hasko G.; Nemeth Z.H.; Vizi E.S.; Salzman A.L.; Szabo C.
 CS G. Hasko, Department of Pharmacology, Institute of Experimental Medicine,
 Hungarian Academy of Sciences, Budapest, Hungary
 SO European Journal of Pharmacology, (9 Oct 1998) 358/3 (261-268).
 Refs: 46
 ISSN: 0014-2999 CODEN: EJPHAZ
 PUI S 0014-2999(98)00619-0
 CY Netherlands
 DT Journal; Article
 FS 030 Pharmacology
 037 Drug Literature Index
 LA English
 SL English
 AB We have recently observed that the selective adenosine A3 receptor
 agonist
 N6-(3-iodobenzyl)-adenosine-5'-N-methyluronamide (IB-MECA) augments
 interleukin-10 and **inhibits** tumor necrosis factor-.alpha.
 production in endotoxemic mice. In the present study, we extended our
 investigations into the effect of this compound on the bacterial
 lipopolysaccharide (endotoxin)-induced inflammatory response in the
 BALB/c, as well as in the C57BL/6 interleukin-10(+/+) and the
 interleukin-10 deficient C57BL/6 interleukin-10(0/0) mice strains. In the
 BALB/c mice, i.p. pre-treatment with IB-MECA (0.2 and 0.5 mg/kg)
 decreased
 lipopolysaccharide (60 mg/kg i.p.)-induced plasma levels of
 interleukin-12
 (p40 and p70), interferon-.gamma., and nitrite/nitrate (breakdown
 products
 of nitric oxide (NO)). On the other hand, pre-treatment with this
 compound
 failed to influence lipopolysaccharide-induced plasma interleukin-
 1.alpha., interleukin-6, and corticosterone concentrations. Similar to
 its
 effect in BALB/c mice, IB-MECA enhanced the release of interleukin-10 in
 the C57BL/6 interleukin-10(+/+) mice. Furthermore, IB-MECA
inhibited the production of interleukin-12, interferon-.gamma.,
 and NO in both the C57BL/6 interleukin-10(+/+) and C57BL/6
 interleukin-10(0/0) mice, suggesting that the **inhibition** of
 pro-inflammatory cytokine production by this compound is independent of
 the increased release of interleukin-10. Finally, pre-treatment with this
 compound protected mice against lipopolysaccharide (60 mg/kg
 i.p.)-induced
 lethality. These results indicate that stimulation of adenosine A3
 receptors has potent anti-inflammatory effects and may represent a
 potential strategy in the treatment of septic shock and other
 inflammatory
 diseases. Copyright (C) 1998 Elsevier Science B.V.
 CT Medical Descriptors:
 *endotoxemia: ET, etiology
 *endotoxemia: TH, therapy
 lethality
 inflammation: ET, etiology
 cytokine release
 septic shock: TH, therapy
 nonhuman
 male
 mouse

animal experiment
 animal model
 controlled study
 intraperitoneal drug administration
 article
 priority journal
 Drug Descriptors:
 *adenosine a3 receptor: EC, endogenous compound
 *adenosine receptor stimulating agent: PD, pharmacology
 *interleukin 12: EC, endogenous compound
 *gamma interferon: EC, endogenous compound
 interleukin 10: EC, endogenous compound
 tumor necrosis factor alpha: EC, endogenous compound
 bacterium lipopolysaccharide: TO, drug toxicity
 6 n (3 iodobenzyl)adenosine 5' n methylcarboxamide: PD, pharmacology
 nitric oxide: EC, endogenous compound
 nitrite: EC, endogenous compound
 nitrate: EC, endogenous compound
 interleukin 1alpha: EC, endogenous compound
 interleukin 6: EC, endogenous compound
 corticosterone: EC, endogenous compound

L22 ANSWER 13 OF 27 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
 AN 1998285863 EMBASE
 TI Vasoactive intestinal peptide **inhibits** IL-12 and nitric oxide
 production in murine macrophages.
 AU Xin Z.; Sriram S.
 CS S. Sriram, Multiple Sclerosis Research Lab., Vanderbilt Stallworth Rehab.
 Hosp., 2201 Capers Avenue, Nashville, TN 37212, United States.
 srirams@ctrvax.vanderbilt.edu
 SO Journal of Neuroimmunology, (14 Aug 1998) 89/1-2 (206-212).
 Refs: 43
 ISSN: 0165-5728 CODEN: JNRIDW
 PUI S 0165-5728(98)00140-4
 CY Netherlands
 DT Journal; Article
 FS 008 Neurology and Neurosurgery
 026 Immunology, Serology and Transplantation
 LA English
 SL English
 AB Vasoactive intestinal peptide (VIP) is a naturally occurring neuropeptide
 widely distributed in the nervous system. In this study, we investigated
 the effect of VIP on IL-12, TNF alpha and nitric oxide (NO) production in
 macrophages following activation with lipopolysaccharide (LPS) or
 superantigens. In vitro studies show that at physiologic concentrations,
 VIP **inhibited** IL-12 and NO but not TNF alpha production in
 macrophages which were stimulated with LPS or superantigens. The
inhibitory effect of VIP on IL-12 production appeared to be cAMP
 mediated since other cAMP inducing agents were also potent in
inhibiting IL-12 production. Since IL-12 plays a critical role in
 T cell function, we suggest that naturally occurring neural hormones can
 regulate the type and direction of the immune response.
 CT Medical Descriptors:
 *peritoneum macrophage
 autoimmune disease: ET, etiology
 macrophage activation
 immunoregulation

immune response
 nervous system
 gastrointestinal tract
 nonhuman
 mouse
 controlled study
 animal cell
 article
 priority journal
 Drug Descriptors:
 *nitric oxide: EC, endogenous compound
 *interleukin 12: EC, endogenous compound
 *vasoactive intestinal polypeptide
 cytokine: EC, endogenous compound
 tumor necrosis factor alpha: EC, endogenous compound
 bacterium lipopolysaccharide
 recombinant interleukin 12
 gamma interferon

L22 ANSWER 14 OF 27 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
 AN 1998284349 EMBASE
 TI Low dose TGF-.beta. attenuates IL-12 responsiveness in murine Th cells.
 AU Gorham J.D.; Guler M.L.; Fenoglio D.; Gubler U.; Murphy K.M.
 CS Dr. K.M. Murphy, Department of Pathology, Washington Univ. School of
 Medicine, 660 South Euclid Ave., St. Louis, MO 63110, United States.
 murphy@immunology.wustl.edu
 SO Journal of Immunology, (15 Aug 1998) 161/4 (1664-1670).
 Refs: 61
 ISSN: 0022-1767 CODEN: JOIMA3
 CY United States
 DT Journal; Article
 FS 026 Immunology, Serology and Transplantation
 037 Drug Literature Index
 LA English
 SL English
 AB Expression of IL-12Rs is one important checkpoint for Th1 development.
 BALB/c DO11.10 CD4+ T cells stimulated by Ag in neutral conditions lose
 expression of the IL-12R .beta.2 subunit and become unresponsive to
 IL-12.
 In contrast, B10.D2 or F1 (BALB/c x B10.D2) DO11.10 CD4+ T cells maintain
 IL- 12R.beta.2 expression when stimulated similarly. Here we show that
 the
 loss of IL-12 responsiveness by BALB/c T cells involves the action of
 endogenous TGF- .beta.. BALB/c T cells stimulated in the presence of
 anti-TGF-.beta. specifically maintain IL-12 responsiveness, express
 IL-12R.beta.2 mRNA, and can stimulate nitric oxide production in
 peritoneal exudate cells. Low concentrations of TGF-.beta. added
 exogenously during primary activation of B10.D2 or F1 T cells
 significantly **inhibit** their development of IL-12 responsiveness.
 These effects of anti-TGF-.beta. are dependent on endogenous IFN-.gamma.
 and are **inhibited** by exogenously added IL-4. Thus, at least one
 effect of TGF-.beta. on Th1/Th2 development may be the attenuation of
 IL-12R.beta.2 expression.
 CT Medical Descriptors:
 *t lymphocyte activation
 *immunoregulation
 protein expression

antigen binding
peritoneum exudate
inhibition kinetics
binding affinity
concentration response
nonhuman
mouse
controlled study
animal tissue
animal cell
article

priority journal
Drug Descriptors:

*recombinant transforming growth factor beta: DO, drug dose
*recombinant transforming growth factor beta: PD, pharmacology
***interleukin 12: EC, endogenous compound**
*interleukin 12 receptor: EC, endogenous compound
messenger rna: EC, endogenous compound
nitric oxide: EC, endogenous compound
gamma interferon: EC, endogenous compound
recombinant interleukin 4: PD, pharmacology

L22 ANSWER 15 OF 27 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN 1998263227 EMBASE
TI Phagocytosis of Leishmania mexicana amastigotes by macrophages leads to a sustained suppression of IL-12 production.
AU Weinheber N.; Wolfram M.; Harbecke D.; Aebischer T.
CS T. Aebischer, Max-Planck-Institut fur Biologie, Abteilung Membranbiochemie, Corrensstrasse 38, D-72076 Tubingen, Germany. Toni.Aebischer@tuebingen.mpg.de
SO European Journal of Immunology, (1998) 28/8 (2467-2477).
Refs: 42
ISSN: 0014-2980 CODEN: EJIMAF
CY Germany
DT Journal; Article
FS 026 Immunology, Serology and Transplantation
LA English
SL English
AB Healing of leishmaniases is dependent on activation of parasitized macrophages (M.PHI.) by IFN-.gamma., which is secreted by Leishmania-specific Th1 cells. IL-12 enhances IFN-.gamma. production by Th1 cells and is crucial for cure. The host cells of Leishmania sp., M.PHI., are a main source of IL-12 in vivo. We report that infection of quiescent murine M.PHI. with L. mexicana or L. major amastigotes does not induce IL-12 production. Moreover, infection suppresses IL-12 secretion
by M.PHI. activated by LPS, by CD40 cross-linking or cognate interaction
with Th1 cells. IL-12 secretion is also suppressed in M.PHI. activated after phagocytosis of latex beads. Suppression is independent of engagement of CR3 or Fc.gamma.R during phagocytosis, is not mediated by IL-10 and does not alter steady state IL-12p40 mRNA levels. In addition, suppression of IL-12 secretion does not depend on M.PHI. activation concurrent to infection. In contrast, NO production was not inhibited. Thus, M.PHI. effector functions are differentially affected and this may be a general effect of phagocytosis of non-activating particles. The possible implications of this effect on the infection are discussed.

CT Medical Descriptors:

*amastigote
 *phagocytosis
 *macrophage
 *leishmaniasis
 cytokine production
 leishmania mexicana
 helper cell
 host cell
 nonhuman
 female
 mouse
 animal experiment
 animal model
 controlled study
 article
 priority journal
 Drug Descriptors:
 *interleukin 12: EC, endogenous compound
 nitric oxide: EC, endogenous compound
 cd40 antigen: EC, endogenous compound
 messenger rna: EC, endogenous compound

L22 ANSWER 16 OF 27 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.

AN 1998117320 EMBASE

TI Mice lacking inducible nitric-oxide synthase are more susceptible to herpes simplex virus infection despite enhanced Th1 cell responses.

AU MacLean A.; Wei X.-Q.; Huang F.-P.; Al-Alem U.A.H.; Chan W.L.; Liew F.Y.

CS F.Y. Liew, Department of Immunology, University of Glasgow, Glasgow G11 6NT, United Kingdom. f.y.liew@clinmed.gla.ac.uk

SO Journal of General Virology, (1998) 79/4 (825-830).

Refs: 29

ISSN: 0022-1317 CODEN: JGVIA Y

CY United Kingdom

DT Journal; Article

FS 004 Microbiology

026 Immunology, Serology and Transplantation

029 Clinical Biochemistry

LA English

SL English

AB Mice deficient in the inducible nitric-oxide synthase (iNOS), constructed by gene-targeting, were significantly more susceptible to herpes simplex virus (HSV)-1 infection, displayed a delayed clearance of virus from the dorsal root ganglia (DRG) and exhibited an increase in the frequency of virus reactivation in DRG compared with similarly infected heterozygous mice. The infected iNOS-deficient mice developed enhanced Th1-type immune responses and their spleen cells produced higher concentrations of IL-12 than similarly infected heterozygous mice. This finding suggests that

iNOS plays an important role in resistance against HSV-1 infection. Furthermore, nitric oxide (NO) may block the development of Th1 cells via **inhibition** of IL-12 synthesis and thereby play a role in immune regulation.

CT Medical Descriptors:

*helper cell
 *herpes simplex virus
 gene targeting

spinal ganglion
spleen cell
cytokine production
enzyme deficiency
infection sensitivity
nonhuman
mouse
animal experiment
controlled study
animal cell
article
priority journal

Drug Descriptors:

*nitric oxide synthase: EC, endogenous compound

*interleukin 12: EC, endogenous compound

L22 ANSWER 17 OF 27 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN 1998071858 EMBASE
TI Suppression of IL-12 production by phosphodiesterase inhibition
in murine endotoxemia is IL-10 independent.
AU Hasko G.; Szabo C.; Nemeth Z.H.; Salzman A.L.; Sylvester Vizi E.
CS E. Sylvester Vizi, Department of Pharmacology, Institute of Experimental
Medicine, Hungarian Academy of Sciences, POB 67, H-1450 Budapest,
Hungary.
ESVIZI@KOKI.HU
SO European Journal of Immunology, (1998) 28/2 (468-472).
Refs: 15
ISSN: 0014-2980 CODEN: EJIMAF
CY Germany
DT Journal; Article
FS 004 Microbiology
026 Immunology, Serology and Transplantation
037 Drug Literature Index
LA English
SL English
AB Phosphodiesterase (PDE) inhibitors are potent regulators of
various immune processes. Immune cells contain type IV and type III PDE.
Here we studied in mice the effects of rolipram, a selective PDE IV
inhibitor, and amrinone, a selective PDE III blocker, on plasma
levels of IL-12 (p70), IFN-.gamma., IL-1, TNF-.alpha., and nitric oxide
(NO) induced by intraperitoneal injection of Escherichia coli
lipopolysaccharide (LPS) (80 mg/kg). Pretreatment of BALB/c mice with
both rolipram (1-25 mg/kg) and amrinone (10-100 mg/kg) decreased plasma IL-12
levels in a dose-dependent manner. Similarly, LPS-elicited plasma
IFN-.gamma. concentrations were suppressed by both rolipram and amrinone.
However, LPS-induced plasma IL-1.alpha. levels were not affected by
either of these compounds. In addition, rolipram inhibited IL-12,
IFN-.gamma., TNF-.alpha. and nitrite/nitrate (breakdown products of NO)
production in C57BL/6 IL-10(+/+) mice as well as in their IL-10-deficient
counterparts (C57BL/6 IL-10(-/-)). Our results suggest that rolipram and
amrinone decrease the immune activation in endotoxemia through
inhibition of the production of pro-inflammatory mediators IL-12,
IFN-.gamma., TNF-.alpha. and NO. These effects are not the consequences
of the increase in IL-10 production by PDE inhibition.

CT Medical Descriptors:

*endotoxemia
nonhuman
male
mouse
animal experiment
article
priority journal
Drug Descriptors:
*interleukin 12: EC, endogenous compound
*interleukin 10: EC, endogenous compound
*rolipram
*amrinone
phosphodiesterase inhibitor
gamma interferon: EC, endogenous compound
interleukin 1: EC, endogenous compound
tumor necrosis factor alpha: EC, endogenous compound
nitric oxide: EC, endogenous compound
escherichia coli lipopolysaccharide

L22 ANSWER 18 OF 27 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.

AN 97245846 EMBASE

DN 1997245846

TI Lipopolysaccharide and monophosphoryl lipid A differentially regulate interleukin-12, gamma interferon, and interleukin-10 mRNA production in murine macrophages.

AU Salkowski C.A.; Detore G.R.; Vogel S.N.

CS S.N. Vogel, Microbiology/Immunology Department, USUHS, 4301 Jones Bridge Rd., Bethesda, MD 20814, United States. vogel@usuhsb.usuhs.mil

SO Infection and Immunity, (1997) 65/8 (3239-3247).

Refs: 67

ISSN: 0019-9567 CODEN: INFIBR

CY United States

DT Journal; Article

FS 026 Immunology, Serology and Transplantation

037 Drug Literature Index

LA English

SL English

AB Monophosphoryl lipid A (MPL) is a nontoxic derivative of the lipid A region of lipopolysaccharide (LPS) that is being developed as both an adjuvant and prophylactic drug for septic shock. We compared the ability of LPS and MPL to induce interleukin-10 (IL-10), IL-12 p35, IL-12 p40, gamma interferon (IFN-.gamma.), glucocorticoid receptor (GR), IL-1 receptor **antagonist** (IL-1ra), and inducible nitric oxide synthase mRNA expression in murine peritoneal macrophages. These genes were chosen for their ability to positively or negatively regulate the host immune response and thus for their potential involvement in MPL-induced adjuvanticity or in its ability to protect against sepsis.

LPS

was a more potent inducer of IL-12 p35, IL-12 p40, and IFN-.gamma. mRNA, as well as of IL-12 protein, than MPL. In contrast, MPL induced higher levels of IL-10 mRNA than did LPS from 1 to 1,000 ng/ml. In general, MPL was not a more potent inducer of negative regulatory genes, since MPL and LPS induced similar levels of GR and IL-1ra mRNA. Addition of anti-IL-10 antibody to cultures increased the induction of MPL-induced IL-12 p35, IL-12 p40, and IFN-.gamma. mRNA, suggesting that the enhanced production of IL-10 by MPL-stimulated macrophages contributes to decreased

production

of mRNA for IL-12 (p35 and p40) and IFN- γ . Conversely, the addition of exogenous IL-10 to LPS-treated macrophages reduced the mRNA expression of these cytokine genes. These studies suggest that enhanced production

of IL-10 by MPL-stimulated macrophages may contribute to the reduced toxicity of MPL through its negative action on induction of cytokines shown to enhance endotoxicity.

CT Medical Descriptors:

*peritoneum macrophage
animal cell

article

cell stimulation

gene induction

mouse

nonhuman

priority journal

Drug Descriptors:

*escherichia coli lipopolysaccharide

*gamma interferon: EC, endogenous compound

*interleukin 10: EC, endogenous compound

*interleukin 12: EC, endogenous compound

*phosphoryl lipid a

cytokine antibody

glucocorticoid receptor: EC, endogenous compound

interleukin 1 receptor blocking agent: EC, endogenous compound

nitric oxide synthase: EC, endogenous compound

L22 ANSWER 19 OF 27 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.

AN 97205418 EMBASE

DN 1997205418

TI Suppression of cyclophosphamide induced diabetes development and pancreatic Th1 reactivity in NOD mice treated with the interleukin (IL)-12

antagonist IL-12(p40)2.

AU Rothe H.; O'Hara R.M. Jr.; Martin S.; Kolb H.

CS Dr. H. Rothe, Diabetes Research Institute, Auf'm Hennekamp 65, D-40225 Dusseldorf, Germany

SO Diabetologia, (1997) 40/6 (641-646).

Refs: 38

ISSN: 0012-186X CODEN: DBTGAI

CY Germany

DT Journal; Article

FS 003 Endocrinology

026 Immunology, Serology and Transplantation

LA English

SL English

AB The macrophage product interleukin (IL)-12 is known to drive Th1 reactions

in physiological and pathological immune responses. Here we report that treatment with the homodimeric IL-12p40 subunit, an **antagonist** of the bioactive IL-12p35/p40 heterodimer, suppresses diabetes

development

in cyclophosphamide-injected NOD mice. Female mice of 70 days old

received

cyclophosphamide (250 mg/kg) to accelerate and synchronize diabetes

development, and daily injections of 1 μ g IL-12(p40)2. While there was no delay of the first diabetes cases, the incidence of overt diabetes was

significantly decreased in treated mice (46 vs 23%, $p < 0.05$). Analysis of mRNA expression in the pancreas showed that administration of the IL-12 **antagonist** had dampened interferon-gamma gene expression, decreased the ratio of interferon-gamma/IL-10 mRNA levels and in parallel suppressed the expression of the inducible nitric oxide synthase. At the same time intra- islet infiltration was significantly decreased ($p < 0.001$). Interestingly, the administration of IL-12(p40)2 also affected IL-12 gene expression, by downregulation of p35 mRNA. We conclude that IL-12 p40 homodimer suppresses diabetes development in the NOD mouse by dampening islet inflammation via selective down-regulation of Th1 type responses. The naturally occurring IL- 12 **antagonist** IL-12(p40)2 represents a new and specific Th1 directed approach to prevent autoimmune diabetes.

CT Medical Descriptors:
 *autoimmunity
 *diabetes mellitus
 *insulinitis
 animal experiment
 animal tissue
 article
 immune response
 macrophage
 mouse
 nonhuman
 pathogenesis
 priority journal
 Drug Descriptors:
 *cyclophosphamide
 *interleukin 12
 gamma interferon
 nitric oxide synthase

L22 ANSWER 20 OF 27 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
 AN 97167915 EMBASE
 DN 1997167915
 TI Neospora caninum: Role for immune cytokines in host immunity.
 AU Khan I.A.; Schwartzman J.D.; Fonseka S.; Kasper L.H.
 CS I.A. Khan, Department of Medicine, Dartmouth Medical School, Hanover, NH 03755, United States
 SO Experimental Parasitology, (1997) 85/1 (24-34).
 Refs: 25
 ISSN: 0014-4894 CODEN: EXPAAA
 CY United States
 DT Journal; Article
 FS 004 Microbiology
 026 Immunology, Serology and Transplantation
 LA English
 SL English
 AB Neospora caninum is a coccidial protozoan parasite that infects a large range of mammals including dogs, cats, mice, and cattle. Morphologically, N. caninum appears indistinguishable from Toxoplasma gondii, although they are genetically distinct. To date there have been no reported cases of this infection in humans, although nonhuman primates may be susceptible to infection. Inbred A/J mice develop no clinical and little histologic

evidence of infection in spite of a high-dose inoculum of *N. caninum*. Splenocytes obtained from infected mice proliferate in vitro in response to both *N. caninum* and *T. gondii*-soluble antigen. A transient state of T cell hyporesponsiveness to parasite antigen and mitogen was observed at Day 7 p.i. This downregulatory response could be partially reversed by the addition of the nitric oxide antagonist LNMMA, but not antibody to IL-10. Mice infected with *N. caninum* produce significant quantities of IL-12 and IFN.γ., most evident shortly after infection. In vivo, antibody to IF-12 is able to neutralize immune resistance to the parasite.

Moreover, in vivo depletion of IFN.γ. with antibody renders the mice susceptible to infection. These observations suggest that *N. caninum* induces a T cell immune response in the infected host that is at least partially mediated by IL-12 and IFN.γ..

CT Medical Descriptors:

*host parasite interaction
 *neospira caninum
 animal experiment
 apicomplexa
 article
 controlled study
 female
 histology
 immunity
 immunosuppressive treatment
 mouse
 nonhuman
 priority journal

Drug Descriptors:

*interleukin 10: EC, endogenous compound
 *interleukin 12: EC, endogenous compound
 *nitric oxide: EC, endogenous compound

L22 ANSWER 21 OF 27 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.

AN 96325754 EMBASE

DN 1996325754

TI Regulation of microglial activation by TGF-β., IL-10, and CSF-1.

AU Lodge P.A.; Sriram S.

CS Multiple Sclerosis Res. Laboratory, Vanderbilt Stallworth Rehabilit Hosp, 2201 Capers Ave, Nashville, TN 37212, United States

SO Journal of Leukocyte Biology, (1996) 60/4 (502-508).

ISSN: 0741-5400 CODEN: JLBIE7

CY United States

DT Journal; Article

FS 008 Neurology and Neurosurgery

026 Immunology, Serology and Transplantation

037 Drug Literature Index

LA English

SL English

AB Microglia are the resident macrophages of the brain and as such are active

participants in immune responses in the central nervous system. Normal resting microglia express low levels of MHC class I and class II antigens and do not produce proinflammatory cytokines. However, microglial immune functions are induced in areas of infection or injury, To understand regulation of cytokines that are secreted by and act upon microglia, we

examined production of interleukin (IL)-12, tumor necrosis factor- α (TNF- α), and nitric oxide (NO) by lipopolysaccharide (LPS)-stimulated microglia. We observed secretion of IL-12, TNF- α , and NO following stimulation of microglia with LPS. Addition of IL-10 suppressed TNF- α , IL-12, and NO production, Transforming growth factor- β (TGF- β) also **inhibited** TNF- α and NO but did not affect IL-12 secretion, IL-12 secretion became sensitive to TGF- β **inhibition** when microglia were cultured in the absence of CSF-1. In addition to its effect on the response to TGF- β , CSF-1 suppressed the response of microglia to LPS. These data suggest

that

CSF-1 may contribute to the immunologically privileged status of the central nervous system.

CT Medical Descriptors:

*macrophage activation

*microglia

article

controlled study

mouse

nonhuman

priority journal

Drug Descriptors:

*colony stimulating factor: PD, pharmacology

*interleukin 10: PD, pharmacology

*interleukin 12: EC, endogenous compound

*nitric oxide: EC, endogenous compound

*transforming growth factor beta: PD, pharmacology

*tumor necrosis factor alpha: EC, endogenous compound

lipopolysaccharide

L22 ANSWER 22 OF 27 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.

AN 96257660 EMBASE

DN 1996257660

TI Interferon- γ . induced type I nitric oxide synthase activity **inhibits** viral replication in neurons.

AU Komatsu T.; Bi Z.; Reiss C.S.

CS Department of Biology, New York University, New York, NY 10003, United States

SO Journal of Neuroimmunology, (1996) 68/1-2 (101-108).

ISSN: 0165-5728 CODEN: JNRIDW

CY Netherlands

DT Journal; Article

FS 004 Microbiology

008 Neurology and Neurosurgery

026 Immunology, Serology and Transplantation

037 Drug Literature Index

LA English

SL English

AB Type I NOS expression increases in OB neurons during VSV infection.

Immunocytochemical Staining of NB41A3 cells indicates constitutive expression of interferon (IFN)- γ receptor and type I NOS.

IFN- γ treatment of NB41A3 cells increased NO production and type 1 NOS protein. In vitro replication of VSV, polio virus type 1, and Herpes Simplex virus type 1 (HSV-1) is significantly **inhibited** by

IFN- γ induced type I NOS and antagonized by NOS **inhibitors**

. In contrast, while IFN- γ treatment **inhibited** influenza and Sindbis virus replication, a different pathway(s) was involved. The

isoform-selective NOS inhibitor, 7-nitroindazole (7NI) was used to treat mice, resulting in a 10-fold higher titer of virus in brain homogenates, and abrogated the recovery-promoting effect of interleukin-12

treatment. Thus, IFN- γ induced type I NOS activity may play an important role in host immunity against neurotropic viral infections.

CT Medical Descriptors:

*nerve cell
 *vesicular stomatitis virus
 *virus infection: ET, etiology
 *virus infection: DT, drug therapy
 *virus inhibition
 animal experiment
 article
 controlled study
 immunocytochemistry
 mouse
 nonhuman
 priority journal
 virus replication
 Drug Descriptors:
 *7 nitroindazole: PD, pharmacology
 *gamma interferon: PD, pharmacology
 *indazole: PD, pharmacology
 *interleukin 12: PD, pharmacology
 *nitric oxide: EC, endogenous compound
 *nitric oxide synthase: EC, endogenous compound
 recombinant gamma interferon: PD, pharmacology
 recombinant interleukin 12: PD, pharmacology
 unclassified drug

L22 ANSWER 23 OF 27 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.

AN 96137575 EMBASE

DN 1996137575

TI The role of interleukin 12 and nitric oxide in the development of spontaneous autoimmune disease in MRL/MP-lpr/lpr mice.

AU Huang F.-P.; Feng G.-J.; Lindop G.; Stott D.I.; Liew F.Y.

CS Department of Immunology, Western Infirmary, University of Glasgow, Glasgow

G11 6NT, United Kingdom

SO Journal of Experimental Medicine, (1996) 183/4 (1447-1459).

ISSN: 0022-1007 CODEN: JEMEA V

CY United States

DT Journal; Article

FS 026 Immunology, Serology and Transplantation

LA English

SL English

AB MRL/MP-lpr/lpr (MRL/lpr) mice develop a spontaneous autoimmune disease. Serum from these mice contained significantly higher concentrations of nitrite/nitrate than serum from age-matched control MRL/MP-+/+ (MRL/+), BALB/c or CBA/6J mice. Spleen and peritoneal cells from MRL/lpr mice also produced significantly more nitric oxide (NO) than those from the control mice when cultured with interferon (IFN) γ and lipopolysaccharide (LPS) in vitro. It is interesting to note that peritoneal cells from MRL/lpr mice also produced markedly higher concentrations of interleukin (IL) 12 than those from MRL/+ or BALB/c mice when cultured with the same stimuli. It is striking that cells from MRL/lpr mice produced high

concentrations of NO were cultured with IL-12 and IPS, whereas only low or background levels of NO were produced by similarly cultured cells from MRL/+ or BALB/c mice. The enhanced NO synthesis induced by IFN- γ /LPS

was substantially **inhibited** by anti-IL-12 antibody. In addition, IL-12-induced NO production can also be markedly **inhibited** by anti-IFN- γ antibody, but only weakly **inhibited** by anti-tumor necrosis factor α antibody. The effect of IL-12 on NO production was dependent on the presence of natural killer and possibly T cells. Serum from MRL/lpr mice contained significantly higher concentrations of IL-12 compared with those of MRL/+ or BALB/c control mice. Daily injection of recombinant IL-12 led to increased serum levels of IFN- γ and NO metabolites, and accelerated glomerulonephritis in the young MRL/lpr mice (but not in the MRL/+ mice) compared with controls injected with phosphate-buffered saline alone. These data, together with previous finding that NO synthase **inhibitors** can ameliorate autoimmune disease in MRL/lpr mice, suggest that the high capacity of such

mice to produce IL-12 and their greater responsiveness to IL-12, leading to the production of high concentrations of NO, are important factors in this spontaneous model of autoimmune disease.

CT Medical Descriptors:

*autoimmunity
animal cell
animal model
article
controlled study
glomerulonephritis: ET, etiology
immunopathogenesis
male
mouse
nonhuman
peritoneum cell
priority journal
spleen cell
etiology
Drug Descriptors:
*interleukin 12
*nitric oxide
gamma interferon
lipopolysaccharide

L22 ANSWER 24 OF 27 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.

AN 96100252 EMBASE

DN 1996100252

TI Interleukin-12 and tumor necrosis factor alpha mediate innate production of gamma interferon by group B streptococcus-treated splenocytes of severe

combined immunodeficiency mice.

AU Derrico C.A.; Goodrum K.J.

CS Department of Biological Sciences, Irvine Hall, Ohio University, Athens, OH

45701-2979, United States

SO Infection and Immunity, (1996) 64/4 (1314-1320).

ISSN: 0019-9567 CODEN: INFIBR

CY United States

DT Journal; Article

FS 004 Microbiology
 026 Immunology, Serology and Transplantation
 LA English
 SL English
 AB The existence of interleukin-12-mediated innate immune responses to group B streptococci (GBS) was tested by examining T-lymphocyte-independent gamma interferon (IFN) production in cultured splenocytes from severe combined immunodeficiency mice. Splenocytes were cultured with killed or living GBS for 48 h, and then IFN was measured by enzyme-linked immunosorbent assay. Type III GBS as well as other extracellular bacterial agents of neonatal sepsis (staphylococci and enterococci) induced IFN production, which was enhanced by interleukin-2 and was **inhibited** by neutralizing antibodies to tumor necrosis factor alpha and to mouse interleukin-12. Interleukin-12 bioactivity was present in conditioned medium from GBS-treated adherent macrophages. Adherent peritoneal macrophages and bone marrow-derived natural killer cells from severe combined immunodeficiency mice cultured separately with GBS did not produce IFN, whereas cocultures did produce IFN. Functional macrophage activation was evident by nitric oxide production in GBS-treated splenocyte cultures. The results show that extracellular pathogens such as GBS, similarly to intracellular microbes, induce macrophage interleukin-12 and tumor necrosis factor alpha, which promote natural killer cell secretion of IFN, which then enhances innate phagocyte resistance mechanisms.

CT Medical Descriptors:
 *combined immunodeficiency
 *spleen cell
 *streptococcus agalactiae
 animal cell
 animal model
 article
 colorimetry
 enzyme linked immunosorbent assay
 human
 human cell
 immune response
 macrophage activation
 mouse
 natural killer cell
 nonhuman
 phagocyte
 priority journal
 t lymphocyte
 Drug Descriptors:
 *gamma interferon: EC, endogenous compound
 ***interleukin 12: EC, endogenous compound**
 *tumor necrosis factor alpha: EC, endogenous compound
 interleukin 2
 neutralizing antibody
nitric oxide: EC, endogenous compound

L22 ANSWER 25 OF 27 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
 AN 96094931 EMBASE
 DN 1996094931

TI Bacterial superantigen-induced human lymphocyte responses are nitric oxide dependent and mediated by IL-12 and IFN-.gamma..

AU Sriskandan S.; Evans T.J.; Cohen J.

CS Infect. Diseases/Bacteriology Dept., Royal Postgraduate Medical School, Hammersmith Hospital, Du Cane Road, London W12 ONN, United Kingdom

SO Journal of Immunology, (1996) 156/7 (2430-2435).
ISSN: 0022-1767 CODEN: JOIMA3

CY United States

DT Journal; Article

FS 026 Immunology, Serology and Transplantation

LA English

SL English

AB Bacterial superantigens cause marked proliferation of T cells and release of lymphokines. Nitric oxide, derived from the conversion of L-arginine to L- citrulline, **inhibits** this activation in murine cells. We have now investigated the roles of IL-12, IFN-.gamma., lymphotoxin-.alpha., and nitric oxide during superantigen-induced human lymphocyte activation. Lymphocyte activation was determined by measurement of proliferative responses and lymphokine release. Both toxic shock syndrome toxin-1 from Staphylococcus aureus and recombinant streptococcal pyrogenic exotoxin A induced proliferation and production of IFN-.gamma., lymphotoxin-.alpha., and IL-12 by human mononuclear cells in a time-dependent fashion. The release of IFN-.gamma. was abrogated by a neutralizing Ab to IL-12, but lymphocyte proliferative responses were unaffected. A neutralizing Ab to IFN-.gamma. prevented the release of lymphotoxin-.alpha., but did not affect proliferation. The neutralization of lymphotoxin-.alpha. using two different Abs did not affect IFN-.gamma. release or proliferation. In contrast to previous findings in mice, the arginine analogue, N(G)-monomethyl-L-arginine, significantly **inhibited** both proliferation and lymphokine release by superantigen-stimulated human cells. Thus, the release of lymphotoxin-.alpha. by lymphocytes following superantigen stimulation is dependent upon the presence of IFN-.gamma.; the IFN-.gamma. response is in turn under the control of IL-12. There is no evidence that nitric oxide plays an **inhibitory** role during superantigen-mediated human lymphocyte activation. Indeed, arginine is a prerequisite for such activation.

CT Medical Descriptors:
*septic shock
*superinfection
*t lymphocyte
article
cell proliferation
human
human cell
lymphocyte activation
priority journal
staphylococcus aureus
Drug Descriptors:
*gamma interferon
*interleukin 12
*nitric oxide
*superantigen

AN 96062974 EMBASE
 DN 1996062974
 TI Leishmania promastigotes selectively **inhibit** interleukin 12
 induction in bone marrow-derived macrophages from susceptible and
 resistant mice.
 AU Carrera L.; Gazzinelli R.T.; Badolato R.; Hieny S.; Muller W.; Kuhn R.;
 Sacks D.L.
 CS Laboratory of Parasitic Diseases, NIAID, NIH, Bethesda, MD 20892, United
 States
 SO Journal of Experimental Medicine, (1996) 183/2 (515-526).
 ISSN: 0022-1007 CODEN: JEMEA V
 CY United States
 DT Journal; Article
 FS 004 Microbiology
 005 General Pathology and Pathological Anatomy
 026 Immunology, Serology and Transplantation
 LA English
 SL English
 AB Leishmania major promastigotes were found to avoid activation of mouse
 bone marrow-derived macrophages (BMMo) in vitro for production of
 cytokines that are typically induced during infection with other
 intracellular pathogens. Coexposure of BMMo to the parasite and other
 microbial stimuli resulted in complete **inhibition** of interleukin
 (IL) 12 (p40) mRNA induction and IL-12 release. In contrast, mRNA and
 protein levels for IL-1.alpha., IL-1.beta., tumor necrosis factor (TNF)
 .alpha., and inducible NO synthase (iNOS) were only partially reduced,
 and
 signals for IL-10 and monocyte chemoattractant protein (MCP-1/JE) were
 enhanced. The parasite could provide a detectable trigger for TNF-.alpha.
 and iNOS in BMMo primed with interferon (IFN) .gamma., but still failed
 to
 induce IL-12. Thus IL-12 induction is selectively impaired after
 infection, whereas activation pathways for other monokine responses
 remain
 relatively intact. Selective and complete **inhibition** of IL-12
 (p40) induction was observed using BMMo from either genetically
 susceptible or resistant mouse strains, as well as IL-10 knockout mice,
 and was obtained using promastigotes from cutaneous, visceral, and
 lipophosphoglycan- deficient strains of Leishmania. The impaired
 production of the major physiologic inducer of IFN-.gamma. is suggested
 to
 underlie the relatively prolonged interval of parasite intracellular
 survival and replication that is typically associate with leishmanial
 infections, including those producing self-limiting disease.
 CT Medical Descriptors:
 *leishmania major
 *macrophage activation
 animal cell
 animal tissue
 article
 b lymphocyte
 female
 genetic susceptibility
 immunoregulation
 mouse
 nonhuman
 parasite survival

parasite virulence
 priority journal
 promastigote
 strain difference
 Drug Descriptors:
 *gamma interferon
 *interleukin 12: EC, endogenous compound
 interleukin 10
 interleukin 1alpha
 interleukin 1beta
 messenger rna: EC, endogenous compound
 monocyte chemotactic protein
 nitric oxide synthase
 tumor necrosis factor alpha

L22 ANSWER 27 OF 27 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
 AN 95208485 EMBASE
 DN 1995208485
 TI IL-12 prevents mortality in mice infected with Histoplasma capsulatum
 through induction of IFN-.gamma..
 AU Zhou P.; Sieve M.C.; Bennett J.; Kwon-Chung K.J.; Tewari R.P.; Gazzinelli
 R.T.; Sher A.; Seder R.A.
 CS Building 10, 9000 Rockville Pike, Bethesda, MD 20892, United States
 SO Journal of Immunology, (1995) 155/2 (785-795).
 ISSN: 0022-1767 CODEN: JOIMA3
 CY United States
 DT Journal; Article
 FS 004 Microbiology
 026 Immunology, Serology and Transplantation
 030 Pharmacology
 037 Drug Literature Index
 LA English
 SL English
 AB Histoplasma capsulatum is a pathogenic fungus found in discrete
 geographic
 locations throughout the world. The fungus invades the
 reticuloendothelial
 organs such as the spleen and liver of immunocompetent hosts where it is
 usually controlled. However, in individuals with immune deficiency,
 histoplasmosis is a severe and potentially fatal disease. Resistance to
 this infection is due primarily to a cellular immune response mediated by
 T cells and macrophages. Moreover, IFN-.gamma. is critical in activating
 macrophages to kill the organism. Herein we study the regulation of
 cytokine induction in mice infected with H. capsulatum and the effects of
 IL-12 in the course of infection. Mice infected with H. capsulatum and
 treated with neutralizing Abs to IFN-.gamma., TNF-.alpha., or IL-12
 experienced accelerated mortality, indicating that endogenous production
 of these cytokines plays an important role in response to infection. In
 contrast, mice treated with IL-12 or a neutralizing Ab to IL-4 at the
 initiation of infection had substantially diminished mortality. Moreover,
 mice infected and treated with IL-12 show a two- to threefold increase in
 the amount of IFN-.gamma. following in vitro stimulation with specific H.
 capsulatum Ag compared with the control infected mice. The protective
 effect of IL-12 could be abrogated if a neutralizing Ab to IFN-.gamma.
 was
 given at the same time, demonstrating that the role of IL-12 in
 protection

was mediated by IFN- γ . Additionally, infected mice treated with IL-12 had a severalfold decrease in the colony counts of *H. capsulatum* in spleen cells after 5 days of infection as compared with control animals. Lastly, spleen cells from infected animals treated with IL-12 showed a striking decrease in their proliferative response to mitogen or *H. capsulatum* Ag. Responses could be restored by adding **inhibitors** of IFN- γ or of nitric oxide to the in vitro cultures. The above observations suggest that IL-12 may be useful in immunologic intervention against this opportunistic pathogen.

CT

Medical Descriptors:

- *histoplasma capsulatum
- *histoplasmosis: DT, drug therapy
- *mortality
- animal cell
- animal experiment
- animal model
- article
- cell proliferation
- controlled study
- female
- intraperitoneal drug administration
- mouse
- nonhuman
- priority journal
- spleen cell
- survival

Drug Descriptors:

- *aminoguanidine
- *cytokine: EC, endogenous compound
- *gamma interferon: EC, endogenous compound
- *interleukin 12: DT, drug therapy**
- *interleukin 12: PD, pharmacology**
- *monoclonal antibody
- *neutralizing antibody
- concanavalin a
- fungus antigen
- interferon antibody
- interleukin 4: EC, endogenous compound
- messenger rna: EC, endogenous compound
- nitric oxide: EC, endogenous compound**
- tumor necrosis factor alpha: EC, endogenous compound